Comprehensive Critical Care: Adult

SECOND EDITION

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S. ROB TODD, MD, FACS, FCCM

Society of Critical Care Medicine
The Intensive Care Professionals

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Second Edition

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Part 10: Administrative and Ethical Issues in the Critically Ill

CHAPTER 1

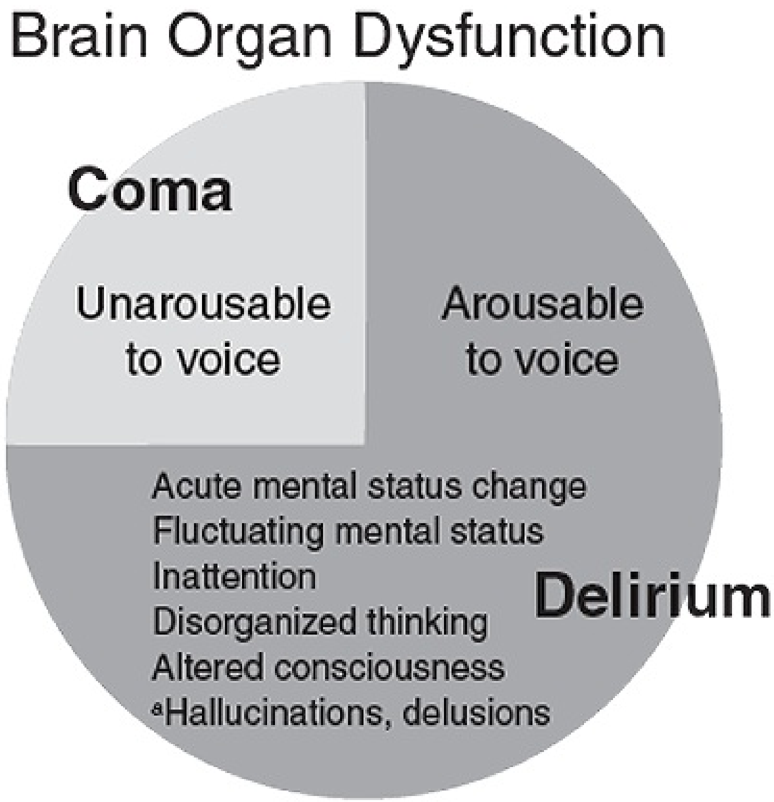
Altered Mental Status During Critical Illness: Delirium and Coma

Stuart McGrane, MBChB, MSCI, Pratik P. Pandharipande, MD, MSCI, and Christopher G. Hughes, MD

Key words: delirium, coma, Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), Richmond Agitation-Sedation Scale (RASS)

Critically ill patients often manifest varying degrees of altered mental status secondary to their acute disease processes or as a consequence of the therapies used to treat disease. These mental status changes range from coma to hyperactive delirium. A comatose patient is unresponsive to physical or verbal stimuli, whereas delirium is an acute and fluctuating disorder of consciousness characterized by inattention, disorganized thinking, and perceptual disturbances (**Figure 1**). Alterations in mental status have traditionally been considered expected consequences of critical illness, and clinicians are increasingly aware that these mental status changes are manifestations of acute brain organ dysfunction that are associated with worse clinical outcomes. Early studies evaluating coma and delirium were hampered by the many different terms (eg, *confusional state, ICU psychosis, acute brain dysfunction*, and *encephalopathy*) used to describe altered mental status during critical illness. Additionally, the lack of validated bedside tools (besides the comprehensive *Diagnostic and Statistical Manual of Mental Disorders*) to diagnose delirium prevented the incorporation of delirium monitoring into routine clinical care in the ICU.

Figure 1. Delineation between delirium and coma, highlighting the cardinal symptoms of delirium



[a]Optional symptoms of delirium (may be present but are not required for the diagnosis of delirium).

DIAGNOSIS OF ACUTE BRAIN DYSFUNCTION

Traditionally, many scales have been available to assess the level of sedation and agitation in ICU patients, including the Ramsay scale, Riker Sedation-Agitation Scale (SAS), motor activity assessment scale, and Richmond Agitation-Sedation Scale (RASS). The recent guidelines on pain, agitation, and delirium from the Society of Critical Care Medicine recommend the use of the RASS and SAS due to their psychometric properties and validity in critically ill patients. The RASS (**Figure 2**) also has been shown to detect variations in the patient's level of consciousness over time or in response to changes in sedative and analgesic drug use. As a first step in assessing the level of consciousness, a sedation-agitation scale should be used. Patients who are unresponsive to verbal commands (eg, a RASS -4 or-5) are considered to be in a coma and cannot be evaluated for delirium at that time. Patients who are responsive to verbal stimuli (eg, RASS -3 and lighter) can further be evaluated for the content of that arousal via the use of delirium monitoring instruments.

Figure 2. The Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tubes or catheters; aggressive	
+2	Agitated	Frequent nonpurposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert but has sustained awakening (eye-opening or eye contact) to *voice* (≥10 seconds)	
-2	Light sedation	Briefly awakens with eye contact to *voice* (<10 seconds)	Verbal Stimulation
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice but movement or eye opening to *physical* stimulation	Verbal Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

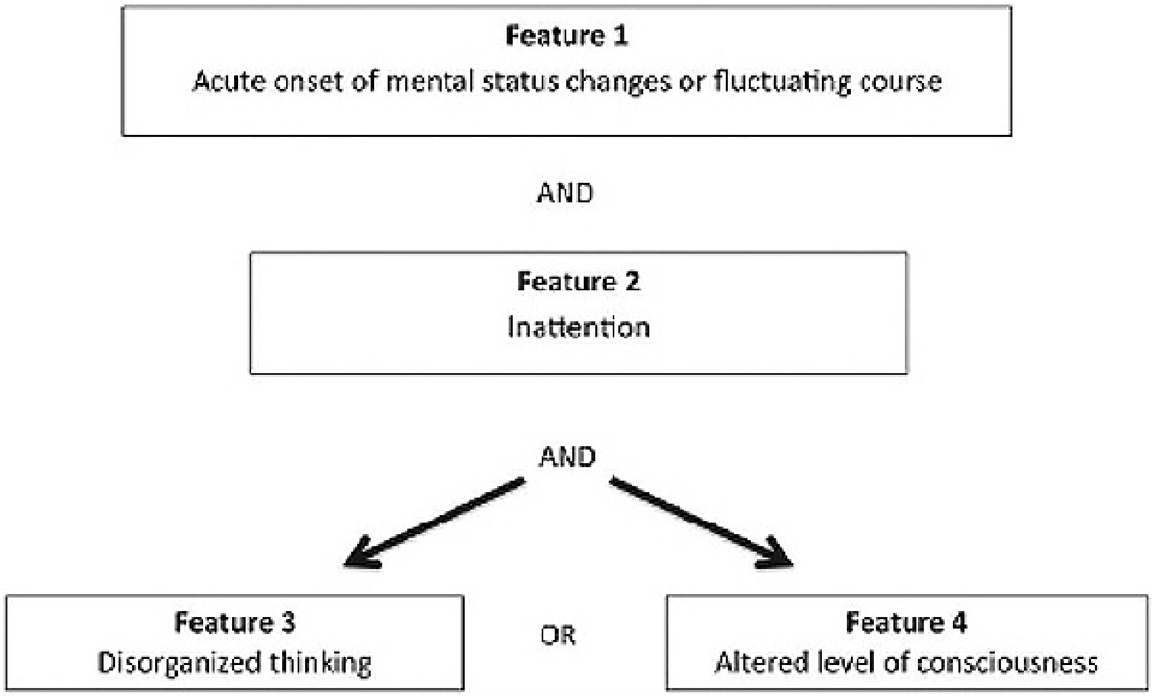
The scale is a 10-point scale with discrete criteria to distinguish levels of agitation and sedation. If RASS is -4 or -5, then stop and reassess the patient at a later time for delirium, since the patient is comatose. If RASS is above -4 (-3 through +4), proceed to delirium assessment. Reproduced with permission from Dr. E. Wesley Ely (www.icudelirium.org).

The validation of the Confusion Assessment Method for the ICU (CAM-ICU) (**Figure 3**) and the Intensive Care Delirium Screening Checklist (ICDSC) (**Table 1**) has resulted in a significant increase in delirium diagnosis, monitoring, and research. The CAM-ICU assesses 4 features of brain function: acute change or fluctuation in mental status (feature 1), inattention (feature 2), disorganized thinking (feature 3), and an altered level of consciousness (feature 4). The diagnosis of delirium using the combination of the RASS scale and the CAM-ICU requires the following:

1. RASS score of -3 or higher *and*
2. Feature 1 of CAM-ICU (acute change or fluctuation in mental status) *and*
3. Feature 2 of CAM-ICU (inattention) *and*

4. One of the following:
    a. Feature 3 (disorganized thinking) *or*
    b. Feature 4 (altered level of consciousness)

Figure 3. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)



Patients are considered to have delirium if they have Richmond Agitation-Sedation Scale scores of -3 and above (see **Figure 2**) and are considered CAM-ICU positive by having features 1 and 2 present and either feature 3 or feature 4 positive.
Adapted with permission the Society of Critical Care Medicine. ICU Liberation. www.iculiberation.org. January 2013.

Table 1. Intensive Care Delirium Screening Checklist[a]

Patient Evaluation	**Characteristics**	**Yes**	**No**
Altered level of consciousness	A: No response (0) B: Response to intense and repeated stimulation (loud voice and pain) (0) C: Response to mild or moderate stimulation (1) D: Normal wakefulness (0) E: Exaggerated response to normal stimulation (1)	1	0
Inattention	Difficulty in following a conversation or instructions Easily distracted by external stimuli Difficulty in shifting focuses	1	0

Disorientation	Any obvious mistake in time, place, or person	1	0
Hallucinations, delusion, psychosis	Unequivocal hallucination or behavior likely due to hallucination or delusion Gross impairment in reality testing	1	0
Psychomotor agitation or retardation	Hyperactivity requiring additional sedative drugs or restraints Hypoactivity or clinically noticeable psychomotor slowing	1	0
Inappropriate speech or mood	Inappropriate, disorganized, or incoherent speech Inappropriate display of emotion related to events or situation	1	0
Sleep-wake cycle disturbance	Sleeping <4 h or waking frequently at night (not initiated by medical staff or loud environment) Sleeping during most of the day	1	0
Symptom fluctuation	Fluctuation of the manifestation of any item or symptom over the course of 24 h	1	0

[a]Total score (0-8). A score ≥4 indicates delirium.

The ICDSC uses 8 diagnostic features to evaluate brain function. A diagnosis of delirium requires 4 or more features from the checklist to be present during the evaluation period. Additionally, patients who have some features from the ICDSC but who do not meet all the requisite criteria for delirium diagnosis are considered to have subsyndromal delirium. This part of the spectrum of acute brain dysfunction has not been fully characterized but likely lies between normal and full feature delirium and is associated with worse outcomes than normal cognition but better outcomes than delirium. A complete description of delirium monitoring tools and training materials (including clinical vignettes and translations of the CAM-ICU) can be found at www.icudelirium.org.

PREVALENCE AND PATHOGENESIS OF BRAIN DYSFUNCTION

The prevalence of acute brain dysfunction in the ICU varies according to the nature and severity of illness in the population studied. Rates of delirium in critically ill, mechanically ventilated patients are upward of 50%, and many studies in medical, surgical, trauma, and burn ICUs report rates between 50% and 80%. Rates of delirium are between 20% and 40% in cardiac ICU patients and in ICU patients with lower severity of illness who do not require mechanical

ventilation. Despite increasing research in the field, the multifactorial pathophysiological process of delirium and coma remains poorly understood. Numerous hypotheses exist and include neurotransmitter imbalance (eg, dopamine, ***y***-aminobutyric acid, and acetylcholine), inflammatory perturbations (eg, tumor necrosis factor α, interleukin 1, and other cytokines and chemokines), endothelial and blood-brain barrier dysfunction, impaired oxidative metabolism, cholinergic deficiency, and changes in various amino acid precursors. Additionally, neuroanatomical changes that include atrophy and white matter track changes have been associated with delirium.

OUTCOMES ASSOCIATED WITH BRAIN DYSFUNCTION

Acute brain organ dysfunction in critically ill patients has been demonstrated to be independently associated with worse clinical outcomes. Patients experiencing delirium have been shown to take longer time to wean from mechanical ventilation. They have increased ICU and hospital length of stay and are more likely to be readmitted to the hospital after discharge. Consequently, the presence of delirium is associated with significantly higher ICU and hospital costs. Furthermore, patients with delirium have higher mortality, and each additional day of delirium is associated with an increased risk of dying. Studies assessing the attributable mortality of delirium in the ICU have found that delirium that persists for 2 or more days increases absolute mortality, but shorter durations of delirium more likely contribute to increased mortality through prolonged ICU length of stay. The outcomes following delirium associated with sedation were recently studied in a cohort of 102 patients. The study defined rapidly reversible sedation-related delirium as delirium that was present while the patient was receiving sedation but that reversed within 2 hours of stopping sedation. This occurred in a small subset of patients (12%), whereas the majority of patients (77%) receiving sedation had persistent, nonreversible delirium. The patients with rapidly reversible delirium had outcomes similar to patients with no delirium, but the patients with persistent delirium had significantly worse outcomes, including increased mortality and institutionalization. This attests to the fact that delirium is not benign, even in patients receiving sedation, and needs to be actively monitored and managed.

Although delirium along with coma represents acute brain dysfunction, many critically ill patients also have long-term cognitive impairment that may persist for months to years after their hospitalization, significantly affecting their quality of life. Among patients who survive their critical illness, upward of 50%

experience long-term cognitive impairment, about a third with deficits in the range of moderate traumatic brain injury and a quarter with deficits similar to those seen in mild Alzheimer's disease. Longer periods of delirium in the hospital are one of the strongest predictors of cognitive impairment 1 year after hospital discharge. This has led the medical profession to place increased attention and emphasis on the prevention and treatment of acute brain organ dysfunction.

RISK FACTORS FOR BRAIN DYSFUNCTION

Contributing sources can be summarized as patient-related factors (eg, age, previous dementia, diabetes, heart failure) or iatrogenic risk factors (eg, psychoactive medications, hypoxemia, shock, hypothermia, sleep deprivation) (**Table 2**). Importantly, sedative regimens, medications, and sleep hygiene are risk factors that may be modifiable by clinicians, and such modifications should be considered in order to decrease the development and/or duration of delirium in critical care patients. The temporal association between psychoactive medications and delirium in critically ill patients has been examined in different ICU cohorts. In a cohort of mechanically ventilated medical ICU patients, lorazepam administration was found to be an independent risk factor for the daily development of delirium after adjustment for important covariates such as age, severity of illness, and presence of sepsis. In surgical, trauma, and burn ICU patients, midazolam has been associated with worse delirium outcomes. The effects of analgesic medications, specifically opioids, on acute brain dysfunction are not as consistently demonstrated as the effects of benzodiazepines. In fact, insufficient pain relief has been shown to be a risk factor for delirium in multiple studies. Prospective cohort studies of patients with hip fractures, none of whom had preoperative delirium, have shown that higher postoperative pain scores are associated with increased incidence and duration of delirium. One study demonstrated that patients who received less than 10 mg of parenteral morphine equivalents per day were more likely to develop delirium than patients who received more analgesia. Additional studies have reported on the beneficial effects of morphine and methadone in delirium. However, providing adequate analgesia needs to be balanced with the potential risk for predisposing patients to delirium due to excess opioid administration, as meperidine and morphine have been associated with increased risk for delirium. Furthermore, strategies to reduce pain through multimodal methods such as regional anesthetic techniques and nonopioid adjuncts have been shown to reduce delirium. Thus, analgesics, including opioids, may be protective of acute brain dysfunction in patients at

high risk for pain but may be detrimental if used excessively to achieve sedation.

Table 2. Risk Factors for Delirium

Host Factors	Acute Illness	Iatrogenic or Environmental
Age	Sepsis	Anticholinergic medications
Baseline comorbidity	Hypoxemia	Sedative medications
Baseline cognitive impairment	Global severity of illness	Analgesic medications
Frailty	Metabolic disturbances	Sleep disturbances

PREVENTION AND MANAGEMENT OF BRAIN ORGAN DYSFUNCTION

To prevent delirium from occurring and to manage its untoward consequences, the clinician must recognize and proactively treat reversible causes of delirium. A partial list of contributing factors in the ICU is shown in **Table 2**. Mnemonics are available to help clinicians remember risk factors. *THINK* stands for Toxic situations, Hypoxemia/hypercarbia, Infection/immobility, Nonpharmacological interventions, and K^+ or other electrolytes. *Dr. DRE* stands for Disease (sepsis, congestive heart failure), Drug Removal (benzodiazepines, antihistamines, anticholinergics), and Environment (remove restraints, orient, mobilize, improve sleep, improve day-night light patterns, etc). Beyond that, just as the potential causes of delirium are multifactorial, the approach to prevention and management must be multifaceted.

Delirium and Coma Prevention

A landmark study of non-ICU medical patients reduced the development of delirium by 40% by focusing on several key goals, including regular provision of stimulating activities, a nonpharmacological sleep protocol, early mobilization activities, appropriate and early removal of catheters and restraints, optimization of sensory input, and attention to hydration. Similar studies have shown a decrease in the duration and severity of delirium without affecting overall incidence; others have shown benefit only in specific subgroups or have not shown any patient benefit. Unfortunately, the efficacy of these nonpharmacological strategies in ICU patients is unknown.

Specific to the ICU population, however, early initiation of physical therapy has

been associated with improved outcomes, including decreased length of stay in both the ICU and the hospital. A randomized controlled study evaluated the combination of daily interruption of sedation with physical and occupational therapy on cognitive and functional outcomes. The investigators demonstrated that patients who underwent early mobilization had an approximate 50% decrease in the duration of delirium in the ICU and hospital and had significant improvement in functional status at hospital discharge. Sleep protocols and improvements in sleep hygiene also have been shown to reduce delirium in ICU patients; however, a double-blind, randomized controlled trial of melatonin versus placebo in patients with hip fracture did not demonstrate a difference in incidence of delirium.

The choice of sedative has implications for acute brain dysfunction beyond the effects of target-based and goal-directed sedation with daily interruption of sedatives. With regard to acute brain dysfunction specifically, the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study (a randomized controlled trial of dexmedetomidine versus lorazepam) provided evidence that sedation with dexmedetomidine can decrease the duration of brain organ dysfunction, with a lower likelihood of delirium development on subsequent days. Comparing dexmedetomidine with midazolam, the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study demonstrated a reduction in delirium prevalence with dexmedetomidine and a shorter time on mechanical ventilation. Another randomized controlled trial, the Dexmedetomidine Compared to Morphine (DEXCOM) study, showed that dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery as compared with morphine-based therapy. Arousability, communication, and patient cooperation were improved with dexmedetomidine sedation versus midazolam and propofol in the Dexmedetomidine Versus Midazolam for Continuous Sedation in the Intensive Care Unit (MIDEX) and Dexmedetomidine Versus Propofol for Continuous Sedation in the Intensive Care Unit (PRODEX) studies. Most recently, a randomized controlled trial of dexmedetomidine versus propofol for ICU sedation after cardiac surgery found a decreased incidence and reduced duration of delirium with dexmedetomidine. This led to a reduction in ICU time and cost related to delirium. These studies attest to the fact that reducing benzodiazepine exposure and use of dexmedetomidine can improve ICU patient outcomes with regard to acute brain dysfunction.

Studies of prophylactic antipsychotic administration to reduce the incidence or

duration of delirium have had mixed results. Perioperative haloperidol prophylaxis in elderly patients undergoing hip surgery did not reduce the incidence of delirium but did decrease its duration. Haloperidol bolus followed by an infusion in elderly patients admitted to the ICU after noncardiac surgery decreased the incidence of delirium only after intra-abdominal surgeries. A before-after study of haloperidol prophylaxis in ICU patients at high risk for delirium showed significantly reduced incidence and duration of delirium. A more recent randomized controlled trial, the Haloperidol Effectiveness in ICU Delirium (HOPE-ICU) study, however, showed no difference in days alive and free of delirium or coma between patients prophylactically treated with intravenous haloperidol or placebo.

Numerous studies have examined agents for delirium prevention after cardiac surgery. A single dose of sublingual risperidone administered when patients regained consciousness reduced the incidence of delirium compared with placebo in one study. Administration of dexamethasone upon induction of anesthesia did not reduce the incidence or duration of delirium in the first 4 days after cardiac surgery. Low cholinergic activity and anticholinergic medications have been associated with delirium, but a randomized controlled trial of rivastigmine versus placebo found no difference in the incidence of postoperative delirium.

The anti-inflammatory effects of statin medications have generated interest in delirium research. Statin therapy while in the ICU has been shown in 2 studies to be associated with lower overall risk of delirium, and increasing duration of statin discontinuation in chronic statin users increases the odds of developing delirium. Further evidence from randomized controlled trials is needed to provide evidence of the ability of statins to prevent delirium.

As a result of increasing evidence of the harm of deep sedation, multiple methods have been evaluated to decrease patients' psychoactive drug exposure. By combining daily spontaneous awakening and breathing trials, the Awakening and Breathing Controlled Trial showed a 50% reduction in sedative use, a reduction in coma and ventilator days during the ICU stay, and, most notably, a reduction in mortality at 12 months. Therefore, a liberation and animation strategy focusing on the ABCDEFs (Assessment and management of pain, Both awakening and breathing trials, Choice of sedation, Delirium monitoring and management, early Exercise, and Family involvement and empowerment) during critical illness can improve patient outcomes and likely can reduce the incidence and duration of acute and long-term brain dysfunction in critically ill patients

(www.iculiberation.org). In fact, a recent study examining a similar bundle demonstrated a significant decrease in delirium and increases in mobilization, days alive, and breathing without assistance.

Delirium Management

Only after correcting contributing factors or underlying physiological abnormalities should the clinician attempt pharmacological therapy to manage delirium. Although numerous studies have examined the effects of antipsychotic medications on delirium, we still lack large randomized controlled trials in the ICU patient population comparing the efficacy of typical and atypical antipsychotics versus placebo. Small studies and case reports, therefore, provide the only data available to guide management recommendations for the antipsychotic medications most suitable for the treatment of delirium.

In one of the first studies specifically evaluating delirium in critically ill patients, olanzapine and haloperidol were shown to be equally efficacious in reducing the severity of delirium symptoms, but the lack of a placebo group makes it difficult to determine whether delirium resolved because of the drugs or because of the passage of time. In a small study of patients with delirium and orders to receive as-needed haloperidol, quetiapine was shown to be more efficacious than placebo in time to resolution of first episode of delirium. Another randomized controlled trial found that a single sublingual dose of risperidone after cardiac surgery reduced the incidence of delirium compared with placebo. The Modifying the Incidence of Delirium (MIND) study compared an atypical antipsychotic (ziprasidone) with a typical antipsychotic (haloperidol) and placebo and found no differences in brain dysfunction outcomes between groups. Rivastigmine was studied as an adjunct to haloperidol; rivastigmine was not found to decrease the duration of delirium and might have contributed to increased mortality.

Two recent studies have examined the role of dexmedetomidine in treating hyperactive delirium. In the Dexmedetomidine to Lessen Intensive Care Unit Agitation (DAHLIA) trial, patients whose weaning from mechanical ventilation was hampered by hyperactive or agitated delirium were randomized to receive up to 7 days of intravenous dexmedetomidine or placebo. Patients treated with dexmedetomidine had increased ventilator-free hours at 7 days and faster resolution of their delirium symptoms. The second study examined nonintubated ICU patients with hyperactive delirium requiring haloperidol for symptom control. Those with improved agitation after haloperidol received a haloperidol

infusion, and those whose agitation did not improve received dexmedetomidine in addition to haloperidol. Patients receiving dexmedetomidine were less likely to fail the regimen, had more time with satisfactory sedation, experienced less oversedation, had a shorter ICU stay, and incurred significantly lower total costs.

Prior to starting medications in an attempt to control a patient's delirium, clinicians should consider discontinuation or dose adjustment of drugs that may be adversely affecting brain function. Although the intended use of these agents is to treat delirium and improve cognition, they all have psychoactive effects that may further cloud the sensorium and promote a longer overall duration of cognitive impairment. Therefore, use of the smallest effective dose given for the shortest necessary time may be the most important delirium management recommendation.

IMPLEMENTING A DELIRIUM MONITORING PROGRAM

When introducing a delirium monitoring program, clinicians must recognize that they are attempting to affect positive change on the prevailing culture. Successful change will start small and grow from there. Many steps are required to ensure success, and lack of attention to detail in any one area may hinder progress. The delirium monitoring program must use a tool that has been validated for the population to be monitored and must incorporate a multidisciplinary approach that includes modern training and learning methods for different learning styles prior to implementation. Some resistance will be encountered, but strategies are available to overcome these (eg, regular feedback sessions, refresher training). Incorporation of delirium data into the medical record and transparent use of this information to effect positive patient outcomes will both encourage and validate those providers who are collecting the information. The presentation of this information on bedside rounds has been referred to as the *brain map*. In this framework, the patient's current brain function and trajectory are reported each day. This should prompt discussion on the patient's overall clinical course and whether the current brain organ function is consistent with the trajectory and other organ functions. These brain map discussions should focus on risk factors (eg, benzodiazepines, sepsis) and possible management strategies (eg, physical therapy, antibiotics).

SUMMARY

Altered mental status (delirium and coma) is a prevalent and costly problem in the critical care patient population that is associated with significant morbidity.

Physicians must strive to balance the need for sedation with the cost that acute and long-term cognitive dysfunction places on both patients and society. With the appropriate attention, diagnostic tools, and medical practice, clinicians have the ability to significantly decrease the burden of this acute brain organ dysfunction. Management techniques with an integrated approach that includes alteration of sedative medication regimens, deployment of preventive strategies, initiation of delirium monitoring, judicious use of pharmacological therapy, early mobility, and improved sleep hygiene can reduce the incidence and impact of this disease in critically ill patients.

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CHAPTER 2

Seizures, Stroke, and Other Neurological Emergencies

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Key words: epilepsy, seizures, stroke, brain injury

STATUS EPILEPTICUS

Status epilepticus (SE) is a common neurological emergency, and it carries significant morbidity and mortality. Traditionally, SE has been defined as continuous or intermittent seizures lasting for more than 30 minutes with incomplete recovery of consciousness. However, the urgency in treating this condition necessitated a more conservative definition.[1] Because there is evidence that tonic-clonic seizures rarely last more than a few minutes, the traditional definition has been discounted. Similarly, animal data suggest that fixed neuronal damage and resistance to pharmacological treatment may occur after 30 minutes of continuous seizing activity. Most experts agree that a patient is in SE if seizures persist for more than 5 minutes or if the patient's state of consciousness does not recover between seizures.

Initial Evaluation and Management

During the initial evaluation, the clinician obtains the patient's relevant information, paying attention to details such as history of brain injury, onset of epilepsy diagnosis, use of antiepileptic drugs (AEDs), use of psychotropic drugs, and history of substance abuse, particularly alcohol. Simultaneous evaluation and management of the airway, breathing, and circulatory state are mandatory within the first 10 minutes of initial assessment. The main principle of critical care management of SE is to treat the seizures quickly and aggressively. About 80% of patients will respond to first-line AEDs if treatment is delivered within 30 minutes of onset, but less than 40% will respond if treated within 2 hours of

onset.

The preferred first-line AED is lorazepam, based on its rapid onset and prolonged action (**Table 1**). Lorazepam is superior to diazepam in controlling seizures at the prehospital and in-hospital levels. In a study by the Veterans Affairs Status Epilepticus Cooperative Study Group,[2] treatment with lorazepam resulted in a 65% success rate versus treatment with phenobarbital (58%), diazepam plus phenytoin (56%), and phenytoin (44%); the proportion of complications, including respiratory depression, was not different among the 4 groups at 30 days. In a landmark randomized controlled clinical trial,[3] respiratory depression was less associated with benzodiazepine use in the management of SE. In the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study, intramuscular midazolam was found to be at least as effective as IV lorazepam in prehospitalized patients with SE.

The preferred second-line agent is phenytoin or fosphenytoin (**Table 1**). Although no strong reason exists for this preference, this AED is the most frequently recommended second-line agent. The efficacy of phenytoin as a second-line agent has been compared with valproic acid. Several newer AEDs such as levetiracetam and lacosamide have been proposed as co-adjuvants in the management of refractory SE (RSE), but more experience is needed before a final recommendation can be made.

Third-line agents should be considered once first and second agents fail (**Table 1**). Intravenous midazolam is the most studied agent for the management of RSE. In a systematic review, Claassen et al[4] reported that the efficacy of midazolam for the treatment of RSE was similar to that of propofol but inferior to that of pentobarbital; however, the use of midazolam was associated with more withdrawal and breakthrough seizures and fewer hemodynamic alterations. The mortality, although high, was similar in all treatment groups. Pentobarbital should be reserved for those patients failing third-line AEDs. It offers great seizure control at the expense of more complications such as hypotension, cardiac depression requiring vasopressors or inotropes, immunosuppression, and longer ICU and hospital length of stay (LOS) based on its longer half-life.

Table 1. Conventional Management Strategy for Status Epilepticus and Refractory Status Epilepticus

Stage	Time	Action	Comments
Resuscitation	0-5 min	Diagnosis ABCs	Obtain ABG, chemistry panel, blood cell counts, AED levels, toxicology tests

		• Airway • Oxygen • Obtain IV access Workup: order EEG	Order ECG Administer thiamine, 100 mg IV Administer Dextrose 50, 25-50 g IV, unless known glucose Consider CT scan in comatose patients particularly if there are lateralizing signs and/or lumbar puncture, but don't delay administration of AEDs or antibiotics.
First-line AED	6-10 min	Lorazepam	Dose: 0.05-0.1 mg/kg over 1-2 min, repeat in 5 min Onset: 3-10 min Effect: 12-24 h Half-life: 14 h Side effects: sedation, respiratory depression (but no different than IV phenytoin), hypotension, hyperosmolar metabolic acidosis with repetitive use secondary to accumulation of propylene glycol. Each milliliter of lorazepam injection (2 mg of lorazepam per milliliter) contains 0.8 mL of propylene glycol.
		Midazolam (IM)	Dose: 0.2 mg/kg IM up to maximum of 10 mg Onset: 2-3 min Effect: 2-4 h Half-life: 2 h Side effects: respiratory depression, hypotension
Second-line AED	11-20 min	PHT or F-PHT	Dose: 20 mg/kg. Rate 150 mg/min (F-PHT), or 25-50 mg/min for PHT to avoid hypotension Onset: 20-25 min Effect: 6-8 h Half-life: 6 h Side effects: 5 to 10% of patients receiving F-PHT have hypotension, arrhythmias, respiratory depression, encephalopathy, nystagmus, ataxia, hepatotoxicity, pancytopenia, Stevens-Johnson's syndrome, hypocalcemia (F-PHT)
		Valproic acid (Some experts consider this AED a third-line agent, but data suggest that it may be more effective than phenytoin.) *Alternatives*	Dose: 30-50 mg/kg. Rate 10 mg/min Onset: 20-25 min Effect: 6-8 h Half-life: 6 h Side effects: respiratory depression, hepatotoxicity, thrombocytopenia

		Levetiracetam	Dose: 1,000-4,000 mg IV. Rate 30-60 mg/min
		Phenobarbital	Dose: 20 mg/kg. Rate 50-100 mg/min
		Lacosamide	Dose: 200-400 mg/kg. Rate 40-80 mg/min
Third-line AED	>20 min	*Continuous IV AED* Midazolam	Dose: 0.2-0.4 mg/kg initial bolus, repeat every 5 min until seizure stops to a total loading dose of 2 mg/kg. IV infusion 0.1 mg/kg to 2 mg/kg/h (maximum 200 mg/h). Side effects: Respiratory depression, hypotension
		Propofol	Dose: 1 mg/kg initial load, repeat 1-2 mg/kg every 3-5 min until seizures stop to a total loading dose of 10 mg/kg. IV infusion 1-15 mg/kg/h. (Do not exceed 5 mg/kg/h for >24 h because this poses a higher risk of propofol infusion syndrome.) Side effects: respiratory depression, hypotension, propofol infusion syndrome (metabolic [lactic] acidosis, rhabdomyolysis, multiple-organ failure)
		Request cEEG	
Fourth-line AED	>60 min	Pentobarbital	Dose: 5 mg/kg initial load, rate 50 mg/min, may repeat 5 mg/kg every 5 min until seizures stop to a total loading dose of 10 mg/kg. IV infusion 1-10 mg/kg/h classically titrated to "burst" suppression. Side effects: respiratory depression, hypotension, immunosuppression, examination compatible with "brain death"

Abbreviations: ABC, airway, breathing, circulation; ABG, arterial blood gas; AED, antiepileptic drug; cEEG, continuous electroencephalography; CT, computed tomography; ECG, electrocardiograph; EEG, electroencephalograph; F-PHT, fosphenytoin; IM, intramuscular; PHT, phenytoin.

ICU Management

Those patients who meet criteria for RSE and require IV AEDs should be admitted to an ICU where continuous electroencephalography (EEG), hemodynamic monitoring, and neurological assessments can be performed hourly. Most neurologists will direct IV AED therapy to a pattern of burst suppression, although directing the therapy to simpler seizure suppression may be an alternative for those intensivists with less experience in EEG monitoring. The two strategies, seizure suppression versus EEG burst suppression, were

compared in a small study that showed no meaningful difference in outcomes. The study suggested that the lack of demonstrable advantage of treatment to burst suppression argues against the routine use of such an aggressive treatment. Additional options for the advanced management of RSE are listed in **Table 2**.

Table 2. Alternatives for the Management of Refractory Status Epilepticus

Antiepileptic drugs	IV levetiracetam Ketamine drip IV lacosamide Lorazepam drip Thiopental Oral topiramate
Anesthetics	Inhaled isoflurane Lidocaine
Miscellaneous medications	Verapamil Acetazolamide Paraldehyde Steroids Corticotropin IV immunoglobulin
Others	Ketogenic diet Vagus nerve stimulation Electroconvulsive therapy Deep brain stimulation Transcranial magnetic stimulation Mild induced hypothermia (33°C-35°C; 91.4°F-95°F)

Information taken from references 12-17.

ISCHEMIC STROKE

Acute ischemic stroke (AIS) is a leading cause of morbidity and mortality in the United States. In 2015, the American Heart Association (AHA) estimated that there were 610,000 new stroke cases, 185,000 recurrent strokes, and 5,700,000 stroke survivors in the United States, many requiring long-term healthcare; in the same year, at least 150,147 deaths were attributed to stroke.

Initial Evaluation and Critical Care Management

The initial evaluation and subsequent ICU management of patients with AIS are based on 5 components: (1) diagnosis; (2) thrombolysis, recanalization, and reperfusion; (3) prevention of infarct expansion, recurrence, and hemorrhagic

conversion; (4) prevention and treatment of malignant cerebral edema; and (5) prevention and management of medical and neurological complications.

Diagnosis

The diagnosis of AIS is made by clinical factors, computed tomography (CT), and magnetic resonance imaging (MRI). Initial neurological evaluation and calculation of the National Institutes of Health Stroke Scale (NIHSS) (**Table 3**) allow for estimation of stroke burden and potential neurological outcome and for objective patient follow-up in the ICU. A noncontrast CT of the brain helps to rule out intracranial mass lesions and hemorrhages. MRI is used in some centers as part of early diagnostic and management algorithms in AIS. The use of telemedicine has the potential to improve the accuracy in diagnosis of AIS.

Table 3. The National Institutes of Health Stroke Scale (NIHSS)

NIH Stroke Scale Item	Scoring Definitions	Score
1a. LOC	0 – alert and responsive 1 – arousable to minor stimulation 2 – arousable only to painful stimulation 3 – reflex responses or unarousable	
1b. LOC Questions—Ask pt's age and month. Must be exact.	0 – Both correct 1 – One correct (or dysarthria, intubated, foreign lang) 2 – Neither correct	
1c. Commands—open/close eyes, grip and release non-paretic hand, (Other 1-step commands or mimic ok)	0 – Both correct (ok if impaired by weakness) 1 – One correct 2 – Neither correct	
2. Best Gaze—Horizontal EOM by voluntary or Doll's.	0 – Normal 1 – partial gaze palsy; abnl gaze in 1 or both eyes 2 – Forced eye deviation or total paresis which cannot be overcome by Doll's.	

3. Visual Field—Use visual threat if nec. If monocular, score field of good eye.	0 – No visual loss 1 – Partial hemianopia, quadrantanopia, extinction 2 – Complete hemianopia 3 – Bilateral hemianopia or blindness	
4. Facial Palsy—If stuporous, check symmetry of grimace to pain.	0 – Normal 1 – minor paralysis, flat NLF, asymm smile 2 – partial paralysis (lower face – UMN) 3 – complete paralysis (upper & lower face)	
5. Motor Arm—arms outstretched 90 deg (sitting) or 45 deg (supine) for 10 secs. Encourage best effort. Circle paretic arm in score box	0 – No drift × 10 secs 1 – Drift but doesn't hit bed 2 – Some antigravity effort, but can't sustain 3 – No antigravity effort, but even minimal mvt counts 4 – No movement at all X – unable to assess due to amputation, fusion, fx, etc.	L or R
6. Motor Leg—raise leg to 30 deg supine × 5 secs.	0 – No drift × 5 secs 1 – Drift but doesn't hit bed 2 – Some antigravity effort, but can't sustain 3 – No antigravity effort, but even minimal mvt counts 4 – No movement at all X – unable to assess due to amputation, fusion, fx, etc.	L or R
7. Limb Ataxia—check finger-nose-finger; heel-shin; and score only if out of proportion to paralysis	0 – No ataxia (or aphasic, hemiplegic) 1 – ataxia in upper or lower extremity 2 – ataxia in upper AND lower extremity X – unable to assess due to	L or R

	amputation, fusion, fx, etc.	
8. Sensory—Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke-related losses.	0 – Normal 1 – mild-mod unilateral loss but pt aware of touch (or aphasic, confused) 2 – Total loss, pt unaware of touch. Coma, bilateral loss	
9. Best Language—Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis	0 – Normal 1 – mild-mod aphasia; (diff but partly comprehensible) 2 – severe aphasia; (almost no info exchanged) 3 – mute, global aphasia, coma. No 1 step commands	
10. Dysarthria—read list of words	0 – Normal 1 – mild-mod; slurred but intelligible 2 – severe; unintelligible or mute X – intubation or mech barrier	
11. Extinction/Neglect—simultaneously touch patient on both hands, show fingers in both vis fields, ask about deficit, left hand.	0 – Normal, none detected. (vis loss alone) 1 – Neglects or extinguishes to double simult stimulation in any modality (vis, aud, sens, spatial, body parts) 2 – profound neglect in more than one modality	

Information taken from National Institute of Neurological Disorders and Stroke (NINDS). National Institute of Neurological Disorders and Stroke (NINDS). http://www.ninds.nih.gov. Accessed June 15, 2016.

Thrombolysis and Recanalization

After 1995, the treatment of AIS was revolutionized by the results of the National Institutes of Neurological Disorders and Stroke (NINDS) trial.[5] Intravenous recombinant tissue plasminogen activator (r-tPA) was initially approved in the United States for use in eligible patients within 3 hours of AIS onset. The recent results of the European Cooperative Acute Stroke Study (ECASS-III) trial confirmed the safety and efficacy of IV r-tPA in AIS patients

within 4.5 hours of onset.[6] Recent clinical trials have demonstrated that endovascular reperfusion of acutely occluded large cerebral arteries through mechanical thrombolysis improves mortality and functional outcome in eligible AIS patients. The maximal time window for successful clinical recovery after reperfusion is within 6 to 8 hours for middle cerebral artery (MCA) or internal carotoid artery (ICA) occlusions and possibly 12 to 24 hours for basilar artery occlusions.

Prevention of Infarct Expansion, Recurrence, or Hemorrhagic Conversion

This phase is achieved by tight blood pressure control, temperature regulation, glycemic control, and secondary stroke prevention. Studies have reported a U-shaped relationship where poor outcome was associated with especially low and especially high admission blood pressure levels. Current guidelines from the AHA and the American Stroke Association recommend withholding antihypertensive therapy for AIS unless there is planned thrombolysis (treat to keep systolic blood pressure [SBP] <180 mm Hg or diastolic blood pressure <105 mm Hg), there is evidence of concomitant noncerebral hypertensive organ damage (eg, acute myocardial ischemia, aortic dissection, pulmonary edema, or renal failure), or the blood pressure is excessively high (SBP >220 or diastolic blood pressure >120 mm Hg), cutoffs that have been arbitrarily determined based on the upper limit of normal cerebral autoregulation.

Hemorrhagic transformation is seen in up to 9% of AIS patients. This devastating complication should be suspected in deteriorating patients with large territorial infarction, cardioembolism, systemic anticoagulation, recent thrombolytic therapy, or uncontrolled hypertension. After administration of IV r-tPA, risk factors for hemorrhagic conversion include a large area of infarction, older age, hyperglycemia, uncontrolled hypertension, congestive heart failure, and prior treatment with aspirin.

Prevention and Treatment of Malignant Cerebral Edema

MCA infarction is associated with higher morbidity and mortality compared to other infarcts. MCA strokes with an NIHSS score of less than 20, thrombus at the carotid terminus location, presence of nausea and vomiting, elevated white blood cell count, early involvement of more than 50% of the MCA territory on CT scans, and additional involvement of the anterior cerebral artery territory and/or posterior cerebral artery territory may be associated with worse edema

and intracranial hypertension (**Figure 1**). Management of cerebral edema and elevated intracranial pressure (ICP) follows the same principles described in **Table 4** for other neurological emergencies. Analgesia, sedation, mechanical ventilation, and hyperventilation should be used to transiently achieve a Pa_{CO_2} of 30 to 35 mm Hg, and hyperosmolar therapy with 20% mannitol or 23.4% saline should be administered. Surgery may offer additional survival benefit to refractory cases of elevated ICP and mass effect.

Figure 1. Left large hemispheric infarct with subfalcine herniation

Table 4. Stepwise Approach for Management of Intracranial Pressure

CSF drainage	Initial CSF drainage may be a lifesaving procedure, particularly in the setting of hydrocephalus and IVH. This technique allows for rapid clearance of CSF, release of ICP, and ICP/CPP monitoring. As a general rule, an ICP monitor or EVD should be placed in all comatose patients (Glasgow Coma Scale score ≤8) with the goal of maintaining ICP <20 mm Hg and CPP >70 mm Hg, unless their condition is so dismal that aggressive ICU care is not warranted. Compared with parenchymal monitors, EVDs carry the therapeutic advantage of allowing CSF drainage and the disadvantage of a substantial risk of infection (approximately 10% during the first 10 days).

Sedation	Sedation should be used to minimize pain and agitation and decrease surges in the ICP. Agitation must be avoided, because it can aggravate ICP elevation through straining (increasing thoracic, jugular venous, and systemic blood pressure), increase $CMRO_2$, and cause uncontrolled hyperventilation or hypoventilation, both of which can be detrimental. During an ICP spike, sedation may be all that is necessary to control the ICP. The goal of sedation should be a calm, comfortable, and cooperative state in patients with ICP that is well controlled, and a quiet, motionless state in patients in whom ICP elevation requires active management. The preferred regimen is the combination of a short-acting opioid such as fentanyl (1-3 μg/kg/h) or remifentanil (0.03-0.25 μg/kg/min) to provide analgesia, and propofol (0.3-3 mg/kg/h) because of its extremely short half-life, which makes it ideal for periodic interruption for neurological assessments; this regimen should be performed daily unless the patient's ICP is too unstable (frequent ICP crisis in the setting of awakening, position changes, fever) to tolerate this. Bolus injections of opioids should be used with caution in patients with elevated ICP because these agents can transiently lower MAP and increase ICP due to autoregulatory vasodilation of cerebral vessels. In one trial, propofol (compared with an opioid-based sedation regimen) was associated with lower ICP and fewer ICP interventions in patients with severe traumatic brain injury. However, propofol has been associated with mitochondrial dysfunction and multiple-organ failure (propofol infusion syndrome). Predisposing factors include young age, severe critical illness of central nervous system or respiratory origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake, and subclinical mitochondrial disease.
CPP optimization	Two prevailing strategies for the management of elevated ICP have evolved from the experience in traumatic brain injury. The Lund concept assumes a disruption of the BBB and recommends manipulations to decrease the hydrostatic BP and increase osmotic pressures in order to minimize cerebral blood volume and vasogenic edema by improving perfusion and oxygenation to the injured areas of the brain. This is achieved in theory by maintaining a euvolemic state with normal hemoglobin, hematocrit, and plasma protein concentrations and by antagonizing vasoconstriction through reduction of catecholamine concentration in plasma and sympathetic outflow. These therapeutic measures attempt to normalize all essential hemodynamic parameters (blood pressure, plasma oncotic pressure, plasma and erythrocyte volumes, PaO_2, and $PaCO_2$).The introduction of microdialysis with novel physiological targets may optimize the goals of the original Lund protocol. The Rosner concept emphasizes maintaining a high CPP to minimize reflex vasodilatation or ischemia at the expense of added cardiopulmonary stress. Computerized bedside graphic displays (eg, the ICU Pilot, CMA Microdialysis, Solna, Sweden) can allow clinicians to identify whether ICP and MAP are positively correlated, in which case a low CPP would be preferable, or negatively correlated, in which case a higher CPP would be desirable.
Hyperosmolar therapy	Hyperosmolar therapy should be used after sedation and CPP optimization fail to normalize ICP. The initial dose of mannitol is 1-1.5 g/kg of a 20% solution, followed by bolus doses of 0.25-1.0 g/kg as needed to a target osmolality of 300-320 mOsm/kg. Additional doses can be given as frequently as once an hour, based on the initial response to therapy with the anticipation of a

	transient decrease in BP. There is little evidence to recommend the use of standing mannitol in patients with normal ICP. Hypertonic saline, such as 23.4% saline solution, can be used as an alternative to mannitol, particularly when CPP augmentation is desirable. However, care should be taken to avoid fluid overload in the setting of heart or kidney failure. The osmotic reflection coefficient of the brain capillaries to sodium is 1.0 compared with 0.9 in the case of mannitol, indicating that HS does not effectively cross the brain capillaries, and over the first few hours of a bolus of HS, the concentration of sodium in the CSF does not change; this forms the basis of efficacy of HS as an osmotic agent effective in brain edema. Additional side effects of hyperosmolar therapy include kidney failure, rebound ICP, electrolytic imbalance (hyponatremia and hypernatremia), and acid-base disturbances. Despite clinical and animal model support, many issues remain to be clarified, including the exact mechanism of action, the best mode and timing of administration, and the most appropriate concentration.
Hyperventilation	Forced hyperventilation is generally used sparingly in the ICU and for brief periods in monitored patients, because its effect on ICP tends to last for only a few hours. Good long-term outcomes can occur when the combination of osmotherapy and hyperventilation is successfully used to reverse transtentorial herniation. Overly aggressive hyperventilation to P_{CO_2} levels <25 mm Hg may cause excessive vasoconstriction and exacerbation of ischemia during the acute phase of ICH and should be avoided. Controlled hyperventilation therapy can be optimized by $SjVO_2$ and $PbtO_2$ monitoring.
Barbiturate coma	For cases of severe and intractable intracranial hypertension, barbiturates can control ICP by decreasing cerebral metabolic activity, which translates into a reduction of the CBF and cerebral blood volume. Pentobarbital can be given in repeated 5 mg/kg boluses every 15-30 min until ICP is controlled (usually 10-20 mg/kg is required) and then continuously infused at 1-4 mg/kg/h. An EEG should be continuously recorded and the pentobarbital titrated to produce a burst-suppression pattern, with approximately 6- to 8-second interbursts, to avoid excessive sedation.
Hypothermia	If pentobarbital fails to control ICP, induced hypothermia to 32°C-34°C (89.6°F-93.2°F) can effectively lower otherwise refractory ICP. Hypothermia can be achieved using various surface and endovascular cooling systems coupled to a rectal, esophageal, pulmonary artery, or bladder thermometer. Complications of hypothermia include nosocomial infection, hypotension, cardiac arrhythmias, coagulopathy, shivering, hyperkalemia, hyperglycemia, and ileus. Because these risks increase with the depth and duration of cooling, some advocate for the induction of mild hypothermia (34°C-36°C; 93.2°F-96.8°F) if temperature reduction is required for a prolonged period of time to control ICP.

Abbreviations: BBB, blood-brain barrier; BP, blood pressure; $CMRO_2$, cerebral metabolic rate of oxygen; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; EEG, electroencephalogram; EVD, external ventricular drain; HS, hypertonic saline; ICP, intracranial pressure; IVH, intraventricular hemorrhage; MAP, mean arterial pressure; $PbtO_2$, brain tissue oxygen tension; $SjVO_2$, jugular venous oxygen saturation.

Decompressive Hemicraniectomy

Four prospective randomized trials investigating the efficacy of decompressive hemicraniectomy (DHC) have been reported. DHC and durotomy more than doubled the chances of survival, from 29% to 78%. This staggering absolute risk reduction of 49% translates into a number needed to treat 2 to avoid 1 fatal outcome. The mortality reduction that results from hemicraniectomy does not come at the cost of an increased risk of survival with severe disability (ie, bedbound and completely dependent). The recently completed Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II (DESTINY-II) clinical trial demonstrated the mortality benefit offered by DHC in patients older than 60 years. In this group age, DHC does not offer a functional or neuroprotective outcome benefit as seen in younger patients (ie, <60 years).

Deep Venous Thrombosis Prophylaxis

Dynamic compression stockings should be placed on admission. After craniotomy, low-dose subcutaneous heparin (5,000 U, 2 or 3 times per day) starting after the second day significantly reduces the frequency of venous thromboembolism, with no increase in intracranial bleeding. Treatment with prophylaxis-dose low-molecular-weight heparin (ie, enoxaparin 40 mg daily) is a reasonable alternative.

Nutrition

As is the case with all critically ill neurological patients, enteral feeding should be started within 48 hours to counteract protein catabolism and malnutrition. A small-bore nasoduodenal feeding tube may reduce the risk of aspiration events. Patients who cannot take food and fluids orally should receive nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing.

Seizure Prophylaxis

The reported frequency of seizures during the first days of stroke ranges from 2% to 23%, but the true risk of seizures appears to be toward the lower end of this range. Seizures are more likely to occur within 24 hours of stroke and are usually partial, with or without secondary generalization. Recurrent seizures develop in 2% to 33% of patients, the rate of late seizures ranges from 3% to

67%, and SE is uncommon. The prophylactic administration of AEDs after stroke is not supported by robust data, so the treatment of seizures after AIS is based on the established management strategies for any neurological illness.

SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) from spontaneous rupture of cerebral aneurysms is the cause of 5% to 10% of strokes annually in the United States (**Figure 2**). Epidemiological studies suggest that the incidence rates of SAH vary substantially worldwide, with the highest rates seen in Japan and Finland. Ruptured berry aneurysms of the base of the brain are the cause of SAH in up to 85% of patients. A so-called benign pattern known as nonaneurysmal perimesencephalic hemorrhage or pretruncal SAH is seen in up to 10% of SAHs, whereas the remaining 5% are caused by various rare conditions (**Table 5**). The mortality after SAH has historically been high, ranging from 30% to 70%, with 10% to 20% of these patients experiencing severe long-term neurological disability; much of this effect is related to the direct effects of hemorrhage and aneurysm rebleeding. The outcome after SAH depends on several factors, including patient age, the severity of the ictus, medical management strategies, and the development of medical complications.

Figure 2. Subarachnoid hemorrhage

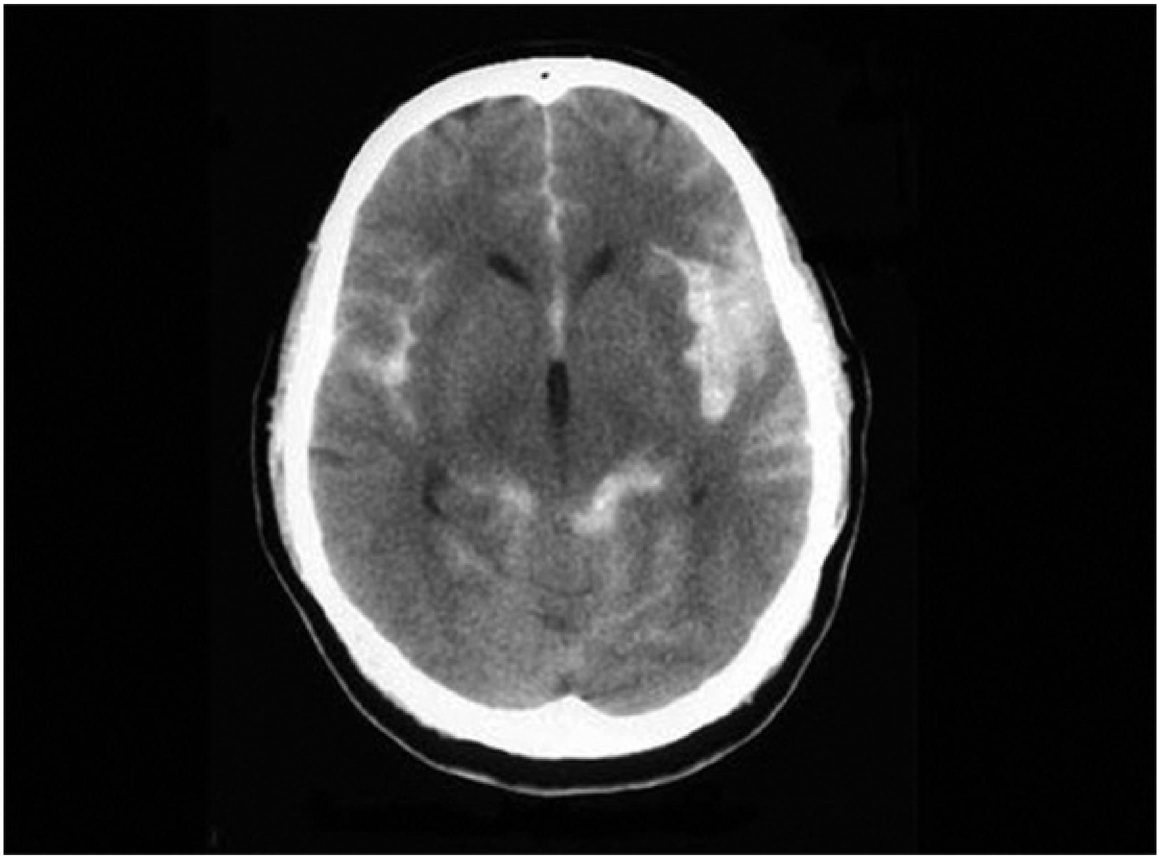


Table 5. Causes of Nonaneurysmal Subarachnoid Hemorrhage

Trauma
Sickle cell disease and coagulopathies
Pituitary apoplexy
Primary or metastatic neoplasms
Drugs • Cocaine • Amphetamines • Anticoagulant or antithrombotic drugs
Inflammatory lesions of cerebral arteries • Mycotic aneurysms (endocarditis) • Beçhet disease • Primary angiitis of the central nervous system • Polyarteritis nodosa • Churg-Strauss syndrome • Wegener's granulomatosis

Noninflammatory lesions of intracerebral vessels

- Arterial dissections
- Arteriovenous malformations
- Cerebral dural arteriovenous fistulas
- Cavernous angiomas
- Cerebral venous thrombosis
- Cerebral amyloid angiopathy
- Moyamoya disease

Vascular lesions of the spinal cord

- Aneurysms of the spinal artery
- Spinal arteriovenous malformations or dural arteriovenous fistulas
- Cavernous angiomas

Initial Evaluation and Management

The management of SAH patients should follow a consistent chronology, with an early phase aimed at stabilizing the cardiopulmonary systems, preventing early rebleeding, and managing hydrocephalus and ICP. This initial phase is followed by a period of vasospasm, during which patients require ICU care and monitoring to prevent delayed cerebral ischemia (DCI) and infarction, and a final subacute period, during which medical or neurological complications of SAH may occur. Comatose, stuporous, or lethargic patients require urgent neurosurgical evaluation for placement of an external ventricular drain. Intravenous fluids and oxygen are administered, and the standard measures of resuscitation need to be deployed: volume resuscitation, maintenance of cerebral perfusion pressure (calculated as mean arterial pressure [MAP] – ICP), blood pressure control, seizure prophylaxis, and pain and agitation control. Seizures at the onset of SAH should be aggressively treated and controlled. Patients with the diagnosis of aneurysmal SAH must be cared for in a high-volume, comprehensive center with neurosurgical and endovascular expertise. In the setting of suspected or elevated ICP, a stepwise approach should be implemented by use of analgesia, sedation, and advanced techniques (**Table 4**).

Targeting Early Rebleeding Risk

The initial goal of SAH care is to limit the risk of rebleeding by blood pressure control, optimization of coagulation parameters or antifibrinolytic therapy, and early aneurysm repair. Most centers actively control elevated blood pressure to a goal SBP of 140 mm Hg or less prior to open surgical or endovascular treatment of the ruptured aneurysm. Extremes of blood pressure on admission (MAP >130

or <70 mm Hg) have also been associated with poor outcome after SAH, so recognition and targeting of early blood pressure derangements may be associated with improved survival. Definitive treatment of the aneurysm is the best anti-rebleeding strategy. Early endovascular treatment and surgical treatment of ruptured aneurysms are acceptable alternatives.

Cerebral Vasospasm

Cerebral vasospasm (cVSP) is a serious medical complication that develops in at least 50% of survivors of SAH (**Figure 3**). With the onset of cVSP, insufficient cerebral blood flow (CBF) reaches affected regions of the brain, causing cerebral ischemia and even stroke (DCI), which could happen in 20% to 30% of patients. Although the cause of cVSP is unknown, neuroinflammatory and vasoconstricting substances originating from blood cell destruction are thought to initiate the process.

Figure 3. Cerebral vasospasm after subarachnoid hemorrhage

The diagnosis of cVSP may be suspected on the basis of changes in the daily neurological examination and variations of transcranial Doppler results, with cerebral angiography serving as the gold standard for its diagnosis. Most often, cVSP begins on day 3 after SAH and reaches its peak on days 6 to 8 after ictus. The symptoms are related to the vascular region of cerebral ischemia, and if cVSP is severe enough and remains untreated, cerebral infarction may occur. Aside from its effect on mortality, one of most important aspects of cVSP is its refractoriness to established medical interventions, emphasizing the need for additional research into the pathophysiological process of SAH-induced cerebrovascular dysfunction.

Risk factors for cVSP are related to the amount of blood seen on admission CT scans. Thick subarachnoid clot on admission CT has been associated with the development of cVSP and DCI after SAH. The Fisher CT grading scale, which evaluates the amount of cisternal blood and the presence of intraventricular

hemorrhage (IVH) or intracerebral hemorrhage (ICH), is widely used to identify patients at high risk for the development of cVSP and DCI (**Table 6**).

Table 6. Risk of Vasospasm According to Fisher and Modified Fisher Grading Systems

Fisher			**Modified Fisher**		
Grade	**Definition**	**Risk of Vasospasm (Symptomatic), %**	**Grade**	**Definition**	**Risk of Vasospasm (Symptomatic), %**
1	No blood	21	0	No SAH or IVH	0
2	Thin blood	25	1	Minimal/thin SAH, no IVH in both ventricles	24
3	Thick blood	37	2	Minimal/thin SAH, with IVH in both ventricles	33
4	Predominantly ICH or IVH	31	3	Thick SAH, no IVH in both ventricles	33
			4	Thick SAH, with IVH in both ventricles	40

Abbreviations: ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.
Information taken from Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke.* 2004;35(2):520-6 and Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29(6):1160-6.

Treatment of Cerebral Vasospasm

Medical treatment in the neurological ICU (NICU) is instituted in all SAH patients and includes intensive hemodynamic support, nutritional support, and prevention of fever, hyperglycemia, and medical complications. Maintenance of normovolemia is key in the initial management of SAH patients. The prophylactic use of the so-called triple-H therapy (hypervolemia, hypertension, hemodilution) is not recommended anymore because the only technique consistently shown to improve CBF is induced hypertension.

Nimodipine is the most widely administered agent after SAH based on its relative selectivity for dilation of the cerebral arteries compared with the

systemic vasculature. Although nimodipine does not appear to decrease angiographic vasospasm, multiple trials have shown that this agent improves outcomes by decreasing the incidence of cerebral ischemia. Angioplasty and intra-arterial vasodilators, either alone or in combination, are the mainstay of therapy for vasospasm after SAH.

Medical and Neurological Complications

Medical complications of SAH are summarized in **Table 7**. These include cardiac arrhythmias and ventricular dysfunction, fever, seizures, hyperglycemia, nosocomial infections (sepsis, pneumonia, ventriculitis, meningitis, among others), and a host of other intrinsic or iatrogenic medical complications such as anemia, elevated ICP, hydrocephalus with shunt dependency, and electrolyte imbalances. Of these complications, rebleeding, DCI, fever, anemia, and hyperglycemia are associated with worse neurological outcomes.

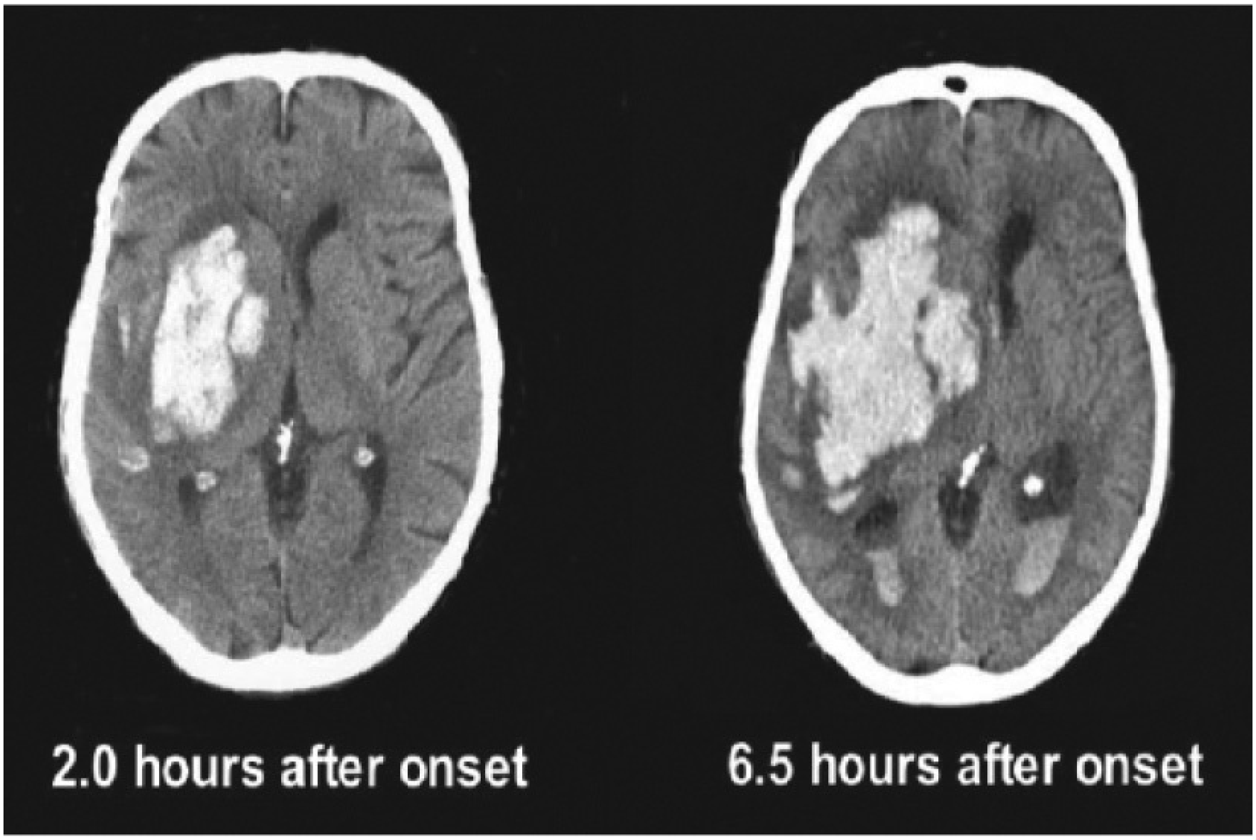
Table 7. Medical and Neurological Complications After Subarachnoid Hemorrhage

Medical complications
Fever (temperature >38.3°C or >100.94°F)
Anemia (hemoglobin <9 mg/dL)
Hyperglycemia
Hypernatremia
Hyponatremia
Infections
Ventilator-associated pneumonia
Bloodstream infection
Urinary tract infections
Cardiac
Hypotension requiring vasopressors and inotropes
Arrhythmias
High cardiac troponin
Decreased left ventricular ejection fraction
Pulmonary
Pulmonary edema
Neurological complications
Seizures
Late hydrocephalus, shunt dependency

INTRACEREBRAL HEMORRHAGE

Nontraumatic forms of ICH account for 10% to 30% of all hospital admissions for stroke (**Figure 4**). Death at 1 year varies by location of the lesion: 51% for deep, 57% for lobar, 42% for cerebellar, and 65% for brain stem hemorrhages. In approximately 40% of cases, blood may extend into the ventricles (IVH), substantially worsening the prognosis and potentially leading to neurological death related to acute obstructive hydrocephalus.

Figure 4. Spontaneous intracerebral hemorrhage



Courtesy of Rincon and Mayer.

Initial Evaluation and Management

Medical therapies for ICH are limited to guidelines or expert opinions regarding blood pressure reduction, ICP monitoring, osmotherapy with fluid resuscitation, fever and glycemic control, and care in a specialized stroke unit or NICU. Recently published guidelines for the management of spontaneous ICH in adults[7,8] provide helpful, evidence-based recommendations.

Diagnosis

Noncontrast CT scan of the brain is the method of choice to evaluate the presence of ICH. CT scan evaluates the size and location of the hematoma, extension into the ventricular system, degree of surrounding edema, and anatomic disruption. Hematoma volume may be easily calculated from CT scan images by use of the ABC2 method, a formula derived from the calculation of the volume of the sphere.

Conventional diagnostic cerebral angiography should be reserved for patients in whom secondary causes of ICH are suspected, such as aneurysms, arteriovenous malformations, cortical vein or dural sinus thrombosis, or vasculitis. Findings on CT scan or MRI that should prompt angiographic study include the presence of SAH, IVH, underlying calcification, or lobar hemorrhage in nonhypertensive younger patients. The role of angiography after ICH has been addressed by 2 studies. Zhu et al[9] reported abnormalities on angiography in 48% of patients who were normotensive and younger than 45 years of age, 49% of patients with lobar hemorrhages, and 65% with isolated IVH; the investigators reported no abnormalities in patients older than 45 years who had a history of hypertension with subcortical ICH. Halpin et al[10] reported finding an underlying lesion in 84% of patients who appeared to have a structural abnormality seen previously on brain imaging. Diagnostic catheter angiography should be strongly considered in all patients with primary IVH and in younger nonhypertensive patients with lobar ICH.

Emergency Department Management

Rapid neurological deterioration and ensuing loss of consciousness with impairment of reflexes that maintain airway protection mandate that airway control be secured. Failure to recognize imminent airway loss may result in complications such as aspiration, hypoxemia, and hypercapnia. Dextrose-containing solutions should be avoided as hyperglycemia may be detrimental to the injured brain. A thorough laboratory panel should be obtained, including hematological, biochemical, and coagulation profiles, and the patient should undergo electrocardiography and chest radiography.

Blood Pressure Control

Blood pressure is frequently elevated in patients with acute ICH, and these elevations in blood pressure are greater than those seen in patients with ischemic stroke. Potential explanations for this phenomenon include upregulation of the neuroendocrine system via the sympathetic nervous system, renin-angiotensin

axis, pituitary-adrenal axis, and increased ICP. The presence or degree of acute hypertension may affect the outcome after ICH. Single-center studies and a systematic review have reported an increased risk of deterioration, death, or dependency with increased admission blood pressure after ICH.

Several clinical trials have evaluated the role of intensive blood pressure reduction after ICH. The phase III clinical trial INTERACT-II (Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) concluded that intensive lowering of blood pressure did not result in a significant reduction in the rate of the primary outcome of death or severe disability. However, a trend was observed when the primary outcome was analyzed in an ordinal fashion, suggesting that in a selected cohort of ICH patients, intensive lowering of blood pressure may improve long-term outcomes. The Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial also confirmed the feasibility and safety of early, rapid blood pressure reduction in ICH without benefit in long-term functional outcome. Both INTERACT and ATACH have shown that while early and intensive blood pressure lowering is clinically feasible and safe, this does not affect clinical outcomes.

Guidelines from the AHA indicate that when SBP exceeds 200 mm Hg or MAP exceeds 150 mm Hg after ICH, management of blood pressure should be achieved with continuous infusion of antihypertensive agents. For those patients with SBP higher than 180 mm Hg or MAP higher than 130 mm Hg and with the possibility of elevated ICP, ICP monitoring should be considered and blood pressure should be lowered using intermittent or continuous IV medications, while maintaining a cerebral perfusion pressure greater than 60 mm Hg. If no elevated ICP is suspected, then targeting a modest reduction of blood pressure is reasonable. In the setting of impaired CBF autoregulation, excessive blood pressure reduction may exacerbate ischemia in the area surrounding the hematoma and worsen perihematomal brain injury. The AHA has recommended that for patients with SBP of 150 to 220 mm Hg, lowering SBP to 140 mm Hg is probably safe.

Preferred agents are β-blockers and calcium channel blockers. Use of nitroprusside has drawbacks, since this agent is associated with a higher rate of medical complications and may exacerbate cerebral edema and ICP. Oral and sublingual agents are not recommended because of the need for immediate and precise blood pressure control. Although no prospective study has addressed the timing of conversion from IV to oral antihypertensive management, this process can generally be started between 24 and 72 hours, as long as the patient's critical

condition has been stabilized.

Initial Emergency ICP Management

Emergency measures for ICP control are appropriate for stuporous or comatose patients or those who present acutely with clinical signs of brainstem herniation (ie, pupillary abnormalities or motor posturing). The patient's head should be elevated to 30°, 1.0 to 1.5 g/kg of 20% mannitol should be administered by a rapid infusion, and the patient should be hyperventilated to a $PaCO_2$ of 26 to 30 mm Hg. As a second-line therapy, or if the patient is relatively hypotensive, 0.5 to 2.0 mL/kg of 23.4% saline solution can be administered through a central venous line. These measures are designed to lower ICP as quickly and effectively as possible, in order to "buy time" before a definitive neurosurgical procedure (craniotomy, ventriculostomy, or placement of an ICP monitor) can be performed. Corticosteroids are contraindicated based on the results of randomized trials that have failed to demonstrate efficacy in ICH. Neurosurgical consultation is warranted for those patients with rapidly declining mental status and hydrocephalus with IVH seen in the initial CT scan. Early placement of a ventricular drain in this case may be lifesaving (**Table 4**).

Hemostatic Therapy

Hematoma size is an important determinant of mortality after ICH, and early hematoma growth, defined as an increase in hematoma size within 6 hours after onset, is consistently associated with poorer clinical outcomes and an increased mortality rate. Similarly, significantly greater reductions in Glasgow Coma Scale and NIHSS scores have been reported among patients with documented hematoma growth on 1-hour follow-up CT scans versus those without growth.

In the phase III Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage (FAST) clinical trial, 80- and 20-µg/kg doses of recombinant activated factor VII were compared against placebo in an overall trial population of 841 ICH patients. No significant difference was found in the main outcome measure, which was the proportion of patients with death or severe disability according to the modified Rankin scale at 90 days (**Table 8**) (score of 5 or 6), but the hemostatic effect and side effect profiles were confirmed. A preliminary clinical study of the antifibrinolytic agent ε-aminocaproic acid was conducted with negative results. The Management of ICH With Aminocaproic Acid open-label pilot study (MANICHAN-PILOT) and the Antifibrinolytic Therapy in Acute Intracerebral Hemorrhage (ATICH)

clinical trial have also been designed to test the hypothesis that ε-aminocaproic acid administration within 3 hours of ICH is associated with less hematoma growth and improved outcomes.

Table 8. The Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Information taken from Banks, J. L. and C. A. Marotta. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3):1091-1096.

Reversal of Anticoagulation

Anticoagulation with warfarin increases the risk of ICH by 5- to 10-fold in the general population, and approximately 15% of ICH cases overall are associated with the use of this agent. Patients with ICH receiving warfarin should be reversed immediately with fresh frozen plasma (FFP) or prothrombin complex concentrate and vitamin K (**Table 9**). Prothrombin complex concentrate contains vitamin K–dependent coagulation factors II, VII, IX, and X; normalizes the international normalized ratio (INR) more rapidly than does FFP; and can be given in smaller volumes but carries a higher risk for development of disseminated intravascular coagulation. In the INR Normalization in Coumadin Associated Intracerebral Hemorrhage (INCH) phase III clinical study, investigators tested the hypothesis that treating coagulopathic ICH with prothrombin complex concentrate would improve normalization of the INR, hematoma growth, and clinical outcomes compared with transfusions of FFP.

The study demonstrated a favorable effect in the form of faster improvement in the INR.

Table 9. Emergency Management of the Coagulopathic Patient With Intracerebral Hemorrhage

Scenario	Agent	Dose	Level of Evidence[a]
Warfarin	Fresh frozen plasma *or*	10-15 mL/kg	II
	3- or 4-factor PCC *and*	15-30 U/kg	II
	Vitamin K	10 mg IV	II
Direct thrombin inhibitor	*Dabigatran*		I
	Activated charcoal within 2 h of ingestion *and*	50 g	
	Idarucizumab *and*	5 g IV (in 2 vials each containing 2.5 g/50 mL)	
	Consider hemodialysis or idarucizumab redosing for refractory bleeding after initial administration		
	Other direct thrombin inhibitors		II
	Activated PCC (FEIBA) *or*	50 U/kg IV	
	4-factor PCC	50 U/kg IV	
Direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban)	Activated charcoal (50 g) within 2 h of ingestion *and*	50 g	III
	Activated PCC (FEIBA) *or*	50 U/kg IV	
	4-factor PCC	50 U/kg IV	

Abbreviations: FEIBA, factor eight inhibitor bypassing activity; PCC, prothrombin complex concentrate.

[a]Class I, based on 1 or more high-quality randomized controlled trials; class II, based on 2 or more high-quality prospective or retrospective cohort studies; class III, case reports and series, expert opinion.

Patients with ICH who have been anticoagulated with unfractionated or low-molecular-weight heparin should be reversed with protamine sulfate, and patients with thrombocytopenia or platelet dysfunction can be treated with a single dose of desmopressin, platelet transfusions, or both (**Table 9**). In patients with abnormal platelet assays and risk of poorer outcome, early platelet transfusion improved platelet activity assay results and was associated with smaller final hemorrhage size and more independence at 3 months. The recently finished Platelet Transfusion in Cerebral Hemorrhage (PATCH) clinical trial demonstrated that platelet transfusion did not improve the risk of hematoma growth and was associated with worse functional outcome in ICH patients who were receiving antiplatelet treatment.

Newer agents such as direct thrombin inhibitors and factor Xa inhibitors provide a new challenge for the reversal of coagulopathy-related ICH. A newly approved antidote is available for the direct thrombin inhibitor dabigatran (**Table 9**). In patients with a strong indication for anticoagulation, such as a mechanical heart valve or atrial fibrillation with a history of cardioembolic stroke, anticoagulation can be safely restarted after 10 days.

ICU Management

Observation in an ICU or a similar setting is strongly recommended for at least the first 24 hours after ictus, since the risk of neurological deterioration is highest during this period and because the majority of patients with brainstem or cerebellar hemorrhage have depressed level of consciousness, requiring ventilatory support. Measurements in the ICU that are indicated for the optimal cardiovascular monitoring of ICH patients include invasive arterial blood pressure, central venous pressure, and, under rare circumstances, pulmonary artery catheter monitoring. An external ventricular drain should be placed in patients with depressed level of consciousness, signs of acute hydrocephalus or intracranial mass effect on CT, and a prognosis that warrants aggressive ICU care.

Patient Positioning

To minimize ICP and reduce the risk of ventilator-associated pneumonia in mechanically ventilated patients, the patient's head should be elevated 30°.

Fluids

Isotonic fluids such as 0.9% saline at a rate of approximately 1 mL/kg/h should be given as the standard IV replacement fluid for patients with ICH and should be optimized to achieve euvolemic balance and an hourly urine output of greater than 0.5 mL/kg. Free water given in the form of 0.45% saline or 5% dextrose in water can exacerbate cerebral edema and increase ICP because the water flows down its osmotic gradient into injured brain tissue. Systemic hyposmolality (<280 mOsm/L) should be aggressively treated with mannitol or 3% hypertonic saline. The use of hypertonic saline in the form of a 2% or 3% sodium chloride–acetate solution (1 mL/kg/h) has become an increasingly popular alternative to normal saline as a resuscitation fluid for patients with significant perihematomal edema and mass effect after ICH. The goal is to establish and maintain a baseline state of hyperosmolality (300-320 mOsm/L) and hypernatremia (150-155 mEq/L), which may reduce cellular swelling and decrease the number of ICP crises. Potential complications of hypertonic saline use are fluid overload, pulmonary edema, hypokalemia, cardiac arrhythmias, hyperchloremic metabolic acidosis, and dilutional coagulopathy. Hypertonic saline should be gradually tapered and the serum sodium level should never be allowed to drop more than 12 mEq/L over 24 hours, to avoid rebound cerebral edema and recurrence of increased ICP.

Prevention of Seizures

Acute seizures should be treated with IV lorazepam (0.05-0.1 mg/kg) followed by a loading dose of phenytoin or fosphenytoin (20 mg/kg) (**Table 1**). An alternative to phenytoin infusion is levetiracetam (500 mg every 12 hours, adjusted for renal insufficiency). Patients with ICH may benefit from prophylactic antiepileptic therapy (AEDs), but no randomized trial has addressed the efficacy of this approach. The AHA guidelines do not recommended antiepileptic medication in the absence of seizures.

Management of Hyperglycemia

Admission hyperglycemia is a potent predictor of 30-day mortality in both diabetic and nondiabetic patients with ICH. In specialized ICU settings, tight glucose control has been linked to reductions in ICP, duration of mechanical

ventilation, and seizures in critically ill neurological patients as well. To minimize the risk of severe hypoglycemia and to avoid worsening possible neuronal damage related to hyperglycemia, it is reasonable to control glucose with targets between 150 and 180 mg/dL.

Management of Elevated ICP

Large-volume ICH carries the risk for development of cerebral edema and high ICP, and the presence of IVH further increases the risk of mortality. This effect is primarily related to the development of obstructive hydrocephalus and alterations of normal cerebrospinal fluid flow dynamics. Patients with large-volume ICH, intracranial mass effect, and coma may benefit from ICP monitoring, although this intervention has not been proven to improve outcomes after ICH. We recommend a stepwise protocol for addressing ICP in the ICU (**Table 4**).

Intraventricular Thrombolytic Therapy

IVH commonly results from extension of ICH into the cerebral ventricular system and is an independent predictor of mortality after ICH. Commonly, hydrocephalus and IVH are managed with an external ventricular drain, but outcomes remain poor. The recently completed Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR-III) trial, a phase III multicenter study, was designed to investigate the effect of administering 1 mg of tPA every 8 hours (up to 12 doses) via an intraventricular catheter in 500 consecutive patients. The study was completed and results are forthcoming.

Surgical Intervention for ICH

Craniotomy has been the most studied intervention for the surgical management of ICH, but the results have been discouraging. The Surgical Trial in Intracerebral Haemorrhage (STICH), a landmark trial of more than 1,000 ICH patients, showed that emergent surgical hematoma evacuation via craniotomy within 72 hours of onset failed to improve outcome compared with a strategy of initial medical management. In contrast to supratentorial ICH, there is much better evidence that cerebellar hemorrhages exceeding 3 cm in diameter benefit from emergent surgical evacuation, given that abrupt and dramatic deterioration to coma can occur within the first 24 hours of onset in these patients. For this reason, it is generally unwise to defer surgery in these patients until further

clinical deterioration occurs.

Because emergent craniotomy has been unable to improve neurological outcome after ICH, the role of other surgical techniques such as minimally invasive surgery has gained importance over the last decade. The advantages of minimally invasive surgery over conventional craniotomy include reduced operative time, the possibility of performance under local anesthesia, and reduced surgical trauma. A recent preliminary analysis of data from the Minimally Invasive Surgery Plus rtPA for Intracerebral Hemorrhage Evacuation (MISTIE) study revealed that the technique was associated with significant reductions in perihematomal edema, cost benefits, and improved outcomes at 1 year.

Hemicraniectomy with duraplasty has been proposed as a lifesaving intervention for several neurological catastrophes such as large hemispheric infarct (LHI) and poor-grade SAH. No randomized controlled trial of this intervention has been conducted in patients with ICH. In a recent report of 12 consecutive patients with hypertensive ICH who were treated with hemicraniectomy, 11 (92%) survived at discharge and 6 of them (54.5%) had a good functional outcome (modified Rankin Scale, 0-3). Another case-control study suggested that patients with ICH associated with significant cerebral edema and an ICH score greater than 2 may potentially benefit from DHC.

Deep Venous Thrombosis Prophylaxis

Like patients with AIS, patients with ICH are at high risk for venous thromboembolism, a potentially fatal complication, due to limb paresis and prolonged immobilization. Prophylaxis strategies are the same as described above for patients with AIS.

NEUROGENIC RESPIRATORY FAILURE

Neuromuscular disorders (NMDs) leading to weakness and mixed respiratory failure may be encountered by the intensivist in the emergency department or ICU. The most important NMDs are myasthenia gravis (MG) with exacerbations or crisis, cholinergic crisis in MG patients, acute inflammatory demyelinating or axonal neuropathies (Guillain-Barre syndrome [GBS], with all variants including the Miller-Fisher variant), Lambert-Eaton myasthenic syndrome, botulism, tick paralysis, organophosphate intoxication, N-hexane (glue sniffing) intoxication, fish poisoning (ciguatera, tetrodotoxin, saxitoxin), myopathies (polymyositis-

dermatomyositis, acid maltase deficiency, critical illness myopathy or neuropathy, undiagnosed mitochondrial myopathies, among others), and magnesium overdoses, particularly in the management of critically ill pregnant women and neurocritical care patients (magnesium may be used as an antishivering agent). In people not vaccinated for diphtheria/pertussis/tetanus or polio, the intensivist might encounter diphtheria or polio-induced neuropathy or neuronopathy.

Initial Evaluation and Management

Establishing a history is important to arrive at a syndromic, anatomic, and possibly etiological diagnosis. Determining whether the patient is really weak or fatigued, malnourished, or just unwilling to cooperate is an important part of the initial evaluation. History of prior crisis or admissions to the hospital is relevant for patients with MG or Lambert-Eaton myasthenic syndrome. Exposure to specific foods, diarrhea or viral illnesses, travel to tick endemic areas, and history of recent vaccinations are important for patients with GBS, tick diseases, or fish poisoning. Absence of vaccination for diphtheria/pertussis/tetanus in particular social groups or residents from abroad who develop upper respiratory tract infections is relevant for the diagnosis of diphtheria or polio. A family history of NMDs is important to establish the diagnosis of certain autosomal dominant or recessive myopathies, neuropathies, and mitochondrial diseases. Particular odors, psychiatric history, or specific findings during the initial evaluation, such as hypersalivation or urinary retention, may help establishing a diagnosis of organophosphate intoxication. Similarly, history of therapeutic high-dose magnesium exposure in an areflexic patient is indicative of magnesium toxicity. Finally, patients with prolonged ICU LOS who are exposed to uncontrolled hyperglycemia, neuromuscular paralysis, gram-negative sepsis, and aminoglycosides, among others, may be at risk for critical illness myopathy or neuropathy.

Initial laboratory studies should include complete blood cell counts, chemistry panel, liver function tests, creatine kinase levels, chest radiograph, electrocardiograph, arterial blood gases, and lumbar puncture for evaluation of cerebrospinal fluid (in case of suspected GBS). Additional urgent testing, based on results of a thorough neurological evaluation, such as brain or spinal cord imaging with CT or MRI, may be important to rule out life-threatening conditions such as basilar thrombosis, brainstem ICH/AIS, and spinal cord compression. Electromyography and nerve conduction studies, although

important, have a low yield during the acute setting for most of the NMDs, so these tests may not be considered urgent in these circumstances.

ICU Management

Patients with suspected acute NMDs, acute on chronic exacerbations of NMDs, or crisis of NMDs should be admitted to an ICU or to an intermediate care or telemetry unit, where vital signs and neurological status can be assessed frequently. The initial assessment of ventilatory function is very important. Patients with NMDs should undergo urgent assessment of respiratory function at the bedside. Vital capacity and the negative inspiratory force may be assessed by a respiratory therapist and should be reassessed frequently. Ventilatory assistance may be required or preferred in those patients with vital capacity less than 15 mL/kg or negative inspiratory forces less than 20 cm H_2O. The arterial blood gases, although informative, are usually unreliable because most patients become acutely hypercarbic or hypoxic only after overt respiratory failure has occurred. Noninvasive intermittent positive pressure ventilation is the most efficient method of increasing alveolar ventilation without intubation.

Myasthenic Specific Treatments

MG is a relatively rare autoimmune disorder of the peripheral nerves in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction. A reduction in the number of acetylcholine receptors induces progressively reduced muscle strength with repeated use of the muscles and reduced recovery of muscle strength following a period of rest. The bulbar or axial muscles are affected most commonly and most severely, but most patients also develop some degree of fluctuating generalized weakness. Myasthenic crisis is characterized by severe axial muscle weakness, abnormalities in the vital signs, and progression to respiratory failure. Cholinergic crisis is also seen and is the result of exaggerated cholinergic activity, usually induced by overdose of anticholinesterase inhibitors (pyridostigmine) and characterized by bradycardia, urinary retention, and increased oral secretions. In early myasthenic crisis, pyridostigmine is typically held since it can aggravate secretions, and underlying precipitants should be addressed and treated accordingly. Rapid treatment with IV immunoglobulin (IVIG) or plasmapheresis is indicated, with both having comparable efficacy, but IVIG may be preferred in patients with hemodynamic compromise, in whom plasmapheresis may be contraindicated. Steroids may be given concomitantly,

but intensivists should expect an exacerbation in muscle weakness within 5 to 10 days after initiation of this therapy in about 50% of patients, of whom 10% will then require mechanical ventilation. The steroid-induced exacerbation tapers off very quickly (within 5-7 days) and may be attenuated by concomitant avoid therapy (IVIG, plasmapheresis). The anticholinesterase inhibitors may be restarted once the patient has improved clinically. Mortality after MG crisis is relatively low (<5%), but the mean duration of mechanical ventilation may be up to 2 weeks. Predictors of prolonged mechanical ventilation and prolonged ICU and hospital LOS include initial HCO_3 greater than 30 mEq/dL, peak vital capacity on days 1 to 6 postintubation less than 25 mL/kg, and older age (>50 years).

Specific Treatments for Guillain-Barre Syndrome

GBS consists of a rare group of immune-mediated polyneuropathies characterized by motor, sensory, and autonomic dysfunction. GBS is the most frequent cause for subacute flaccid, areflexic paralysis in the United States (1-3 per 100,000 people). The origin of GBS is related to molecular mimicry triggered by certain infections and activation of the T-cell–mediated response against ganglioside molecules in the surface of peripheral nerves. Clinical suspicion is raised by the onset of subacute ascending and areflexic paralysis characterized by albumin-cytological dissociation in the cerebrospinal fluid. Similar to MG crisis, GBS requires surveillance of ventilatory function. Treatment with plasma exchange and IVIG has been studied in clinical trials, and these treatments enhance recovery with similar efficacy; corticosteroids are not beneficial. Prognosis is usually good; mortality is lower than 5%, and up to 90% of patients experience full recovery within 6 to 12 months. Predictors of poor outcome include older age, rapid onset, preceding diarrheal disease, respiratory failure, and axonal variants.

Specific Treatments for Critical Illness Polyneuropathy and Critical Illness Myopathy (CIP/CIM)

Critically ill patients are at risk of developing severe weakness secondary to CIP/CIM. The incidence of CIP/CIM in these patients has been estimated to be around 33% to 44%. The incidence may be higher in septic patients, those exposed to neuromuscular blocking agents, those who have used steroids, and those with hyperglycemia. The mortality of CIP/CIM has been reported between 26% and 71%; up to 70% of patients may recover after 6 months, but 30% may have long-term sequelae. Specific therapies to treat this condition are lacking,

but it may be prevented or attenuated by avoiding use of neuromuscular blocking agents, avoiding prolonged use of steroids, and initiating early physical therapy. In one study, tight glycemic control was associated with lower incidence of CIP and fewer ventilator weaning days, suggesting that hyperglycemia may play a role in the pathophysiological process of CIP.

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CHAPTER 3

Critical Care Management of Traumatic Brain Injury

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Key words: traumatic brain injury, hypertonic saline, intracerebral hypertension, clinical practice guidelines, cerebral edema, intracranial pressure, craniectomy, brain code

The clinical management of traumatic brain injury (TBI) continues to evolve. Over the past few decades, recovery from moderate to severe TBI has improved dramatically despite the lack of neuroprotective or neuron-specific rescue medications. This improvement in outcomes can be attributed to aggressive efforts to mitigate secondary injury caused by ischemia, inflammation, and the neuropathological cascade. Outcomes are the fundamental goal of emergency and critical care management of TBI. Achieving this goal involves maintaining general physiological status and averting traumatic intracranial hemorrhage (tICH), cerebral edema, and elevations in intracranial pressure (ICP). A significant advance has been the development and dissemination of evidence-based clinical practice guidelines (CPGs), many of which provide recommendations for management of TBI in an ICU.

TBI is an all-too-common condition. Motor vehicle accidents, falls, assaults, and sports-related accidents are among the most common causes. TBI remains a leading cause of death and disability, particularly among young adults, and it can range in severity from concussion to coma. Most people who sustain mild TBI or concussion can be managed as outpatients, whereas patients with moderate to severe TBI will need admission to an ICU where close neurological monitoring and focused neurological critical care can be applied.

CLASSIFICATION

TBI is classified as mild, moderate, or severe. The Glasgow Coma Scale (GCS) score is used as a critical determinant in classifying patients. Unfortunately, evidence indicates that physician knowledge of the GCS is inadequate.[1] Thus, the GCS should be a routine part of scheduled review and practice. The criteria for determining the GCS are summarized in **Table 1**.

Table 1. Glasgow Coma Scale

Motor	Score	Verbal	Score	Eyes	Score
Follows commands	6	Oriented, alert	5	Eyes open spontaneously	4
Localizes	5	Confused, appropriate	4	Eyes open to voice	3
Withdraws	4	Disoriented, inappropriate	3	Eyes open to pain	2
Flexion	3	Incomprehensible speech	2	No response	1
Extension	2	No response	1		
No response	1				

Information taken from Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;2:81-84.

Mild TBI is determined by an admission GCS score of 13-15, with the vast majority of patients normal (GCS 15). Because patients with mild TBI can appear uninjured, it is important to screen potential TBI victims at the point of injury, such as the playing field or battlefront. Clinical tools are available to aid the first responder in identifying risk of TBI, such as the SCAT-3 (Sports Concussion Assessment Tool, version 3) and the MACE (Military Acute Concussion Examination). Persons found to be at risk of TBI should be immediately removed from competitive play or the combat environment, as appropriate. This is both medically appropriate and in accordance with state laws mandating removal from play or work. At this point, the patient must be referred to an advanced healthcare provider to make the diagnosis, which will be accomplished by history and physical and neurological examinations. Diagnoses of concussion or mild TBI are clinically used interchangeably. However, more precisely, concussion is a clinical syndrome, whereas TBI denotes a pathological state. Patients with mild TBI may present with brief loss of consciousness,

confusion, or amnesia of events prior to their trauma. Diffuse headache, dizziness, and insomnia are some of the more common complaints. Symptoms typically resolve over a few days to weeks. However, a postconcussive syndrome can ensue in which symptoms may last for many months, especially posttraumatic amnesia.[2] Optimal clinical care is outlined by CPGs, which exist for sports[2-4] and combat.[5]

Moderate TBI is indicated by an admission GCS score of 9 to 13 and is usually associated with prolonged loss of consciousness, abnormal findings on neuroimaging, and neurological deficits.[6] The presence of moderate TBI necessitates hospitalization for close neurological observation and potential neurosurgical intervention.

Patients determined to have severe TBI have initial GCS scores of 8 or less. As these patients are significantly neurologically injured, they frequently will have a skull fracture, tICH, or contusion.[6] These patients may also have subdural hematomas (SDHs), epidural hematomas, or traumatic subarachnoid hemorrhage. These patients need to be admitted to a neuro–critical care unit and may require neurosurgical intervention.[7]

CLINICAL PRACTICE GUIDELINES

Outlining treatment of TBI patients in the form of CPGs based on best available evidence has been a major advance in TBI care. The most commonly used CPGs, those published by the Brain Trauma Foundation, provide evidence-based recommendations for the care of patients with TBI.[8] An interactive guideline compliance tool maintained by the Brain Trauma Foundation is available at www.tbiclickandlearn.com. Additional CPGs published by the US Army Institute of Surgical Research,[9] as part of the Joint Theater Trauma System, are available and include the management of severe head trauma, evaluation of the cervical spine, and management of spine and spinal cord injury, among other topics of interest. These CPGs, as well as Advanced Trauma Life Support protocols, are primary resources for providers who treat TBI.[10,11]

CLINICAL EVALUATION

The neurological examination is the best tool for clinically evaluating patients with TBI. According to the Advanced Trauma Life Support CPGs, the resuscitated neurological examination is done as part of the “D” or disability evaluation. This occurs immediately after the ABCs (airway, breathing, and

circulation) are addressed. In the field, first providers should determine a GCS score and pupillary function. Advanced providers should perform a detailed neurological examination that includes assessment of GCS score, level of consciousness, and motor, sensory, and cranial nerve function.[10,12] This should be done before analgesic, sedative, or paralytic agents are administered. Radiographic imaging, blood tests, and, occasionally, cerebrospinal fluid (CSF) analysis offer additional clinical information.

When evaluating a neurologically compromised patient, the clinician must consider that altered mental status or obtundation may be due to non-TBI causes, including impaired ventilation, insufficient oxygenation, hypoperfusion, hypoglycemia, and medication and toxin exposure in addition to head injury. These conditions must be considered during the initial evaluation.[10]

Initial Interventions

Optimal TBI management begins at the scene of injury. Attention to the ABCs is paramount. Injured brain can tolerate severe hypoxia for a very limited period because brain reserves of oxygen last only a matter of minutes. Hypoxia and hypotension in the acute period can have dramatic consequences on the clinical outcome.[8,13] Thus, immediate goals of TBI resuscitation are airway protection, adequate oxygenation, and restoration of brain perfusion. The so-called hypotensive resuscitation is not appropriate in the setting of known head injury.[14]

Prehospital CPGs have been developed for first medical responders.[15,16] An artificial airway should be placed when a patient's GCS score is less than 8. Hypoxia should be avoided by maintaining oxygen saturation greater than 90% or Po_2 greater than 60 mm Hg. Hypotension should be avoided with the goal of keeping systolic blood pressure (SBP) greater than 90 mm Hg. Hyperventilation should be instituted only for clinical evidence of cerebral herniation (discussed subsequently) and not for routine use or for prophylaxis against elevated ICP. Although no specific resuscitation fluid is recommended, hypertonic saline (HTS) is recognized to have significant theoretical advantages in terms of rheology and volume expansion in the setting of trauma. 3% HTS boluses of 500 mL or less are acceptable. The use of HTS to reduce elevated ICP is optional. Mannitol can be administered for cerebral herniation at doses of 0.25 to 1.0 g/kg IV as long as intravascular volume can be maintained. Other interventions include maintaining midline position of the head and elevating the head of the

bed to 30°. This optimizes cerebral venous drainage, which, if compromised, can exacerbate intracranial hypertension.

When cerebral herniation is observed, a “brain code” should be instituted. The brain code consists of elevating the head of the bed to 30°, administering mannitol (0.25-1.0 g/kg IV), and acutely hyperventilating the patient (P_{CO_2} of 30-35 mm Hg). Intravenous administration of 30 mL of 23.4% HTS may be considered if central venous access has been established.

It is prudent to always assume that a patient with TBI has an occult cervical spine injury. The cervical spine should be immobilized with a rigid neck collar during the initial survey, which should be left in place to ensure cervical spine stability and keep the head properly positioned.

The cervical spine can be cleared of injury by an advanced provider using neurological examination. If a patient cannot cooperate with a neurological examination, then cervical spine injury needs to be ruled out by radiographic imaging.[10] Spinal injuries concomitant with TBI are common. A recent retrospective review of head injury casualties from the wars in Iraq and Afghanistan reported a 16% incidence of spinal column trauma of various types.[17]

Neuroimaging

Computed tomography (CT) is the primary neuroimaging modality used for TBI. A noncontrast CT of the head takes just a few minutes to obtain and provides clinically useful data. Indications for head CT include GCS score less than 15, prolonged loss of consciousness (>5 minutes) or antegrade amnesia, clinical evidence of basilar skull fracture, depressed skull fracture greater than 1 cm on clinical examination, penetrating injury, anisocoria or fixed and dilated pupils, any neurological deficit, known bleeding diathesis, and anticoagulant treatment.[18] The decision to obtain a head CT can also be based on risk.[18,19] Signs that indicate high risk for intracranial pathological changes for which a CT is needed include focal neurological deficits, penetrating head wound, palpable depressed skull fracture, and impaired mental status not caused by drugs or other intoxicants. Signs and symptoms of moderate risk include a history of mental status change, progressive headache, seizure, amnesia, clinical evidence of basilar skull fracture, serious facial injury, vomiting, and multiple trauma; a patient who is younger than 2 years and is a possible victim of child abuse is also considered to be at moderate risk. Signs and symptoms that indicate low risk

include headache, dizziness, scalp laceration, scalp hematoma, and lack of signs and symptoms.

Magnetic resonance imaging (MRI) provides greater structural detail than CT. Although MRI has not been shown to affect acute clinical care, MRI can be helpful for prognostication, particularly because brainstem lesions and diffuse axonal injury that are not easily seen on CT may be more clearly identified on MRI. In penetrating TBI, MRI should not be used given the risk of heat and movement of retained foreign bodies by the MRI's high magnetic field.[20] MRI should not be used when a patient is clinically unstable, because clinical monitoring during the study is difficult.

If a cerebrovascular injury is suspected, cerebral angiography is recommended. If vasospasm or other cerebral blood flow issues are of concern, transcranial Doppler or CT angiogram may be used. Transcranial Doppler is a bedside noninvasive test that measures blood flow velocity. As such, transcranial Doppler can provide useful real-time physiological data. For example, it can help diagnose vasospasm, which has a high incidence among patients who have sustained severe TBI due to explosive blast, approaching 50%.[21] Such patients should undergo regular noninvasive transcranial Doppler assessment, and if moderate to severe vasospasm is found, more invasive cerebral angiography can be performed for definitive diagnosis and endovascular-based treatment.[21]

Clinical Syndromes

Patients with severe TBI may develop intracranial hypertension that can progress to cerebral herniation. Because the skull is a rigid container, increases in volume from hemorrhage or edema must be compensated by displacement of blood or CSF. When these compensatory mechanisms are exceeded, the brain is displaced, resulting in cerebral herniation syndrome. Because ICP monitoring is often unavailable, especially during acute management, malignant intracranial hypertension may develop unnoticed. Thus, it is helpful to be aware of the clinical manifestations of increased ICP and brain herniation. When such indicators are present, emergency brain resuscitation or a brain code is indicated.

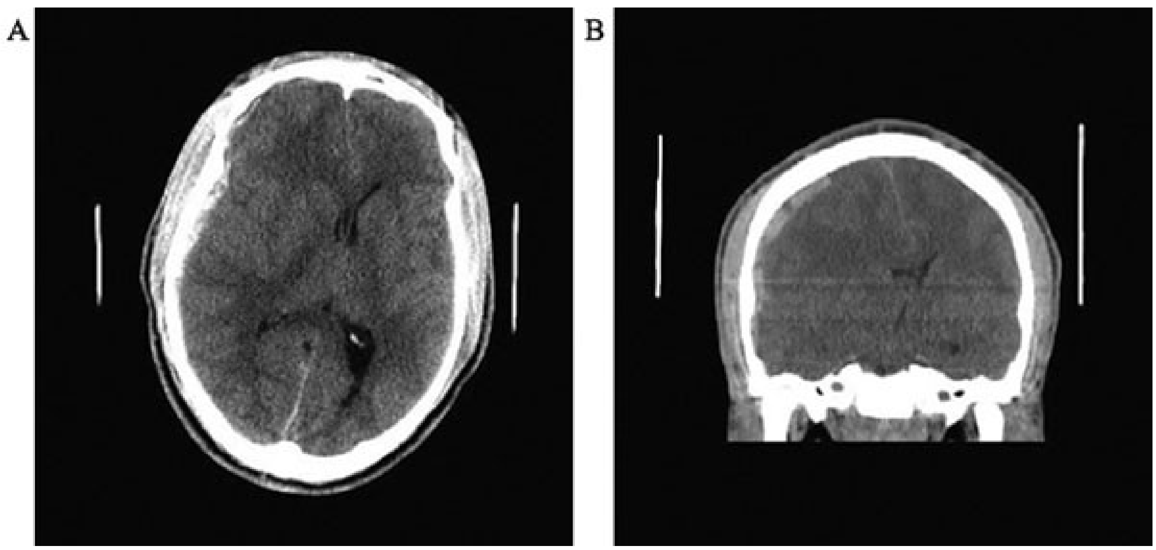
Subfalcine herniation is lateral shift of one frontal lobe into the contralateral side. This type of herniation can occur with any degree of midline shift seen with space-occupying lesions such as SDH, epidural hematoma, cerebral contusions, or intracerebral hemorrhage. The most common clinical manifestations are increasing lethargy and, occasionally, neurological deficits related to

compromised flow to one or both anterior cerebral arteries. Unilateral anterior cerebral artery compromise classically causes weakness of the contralateral lower extremity, although involvement of the proximal arm and shoulder has been reported[22] (**Figure 1**).

Figure 1.

(A) Subfalcine herniation in a patient with an acute subdural hematoma, axial head computed tomography (HCT)

(B) Coronal HCT of same patient

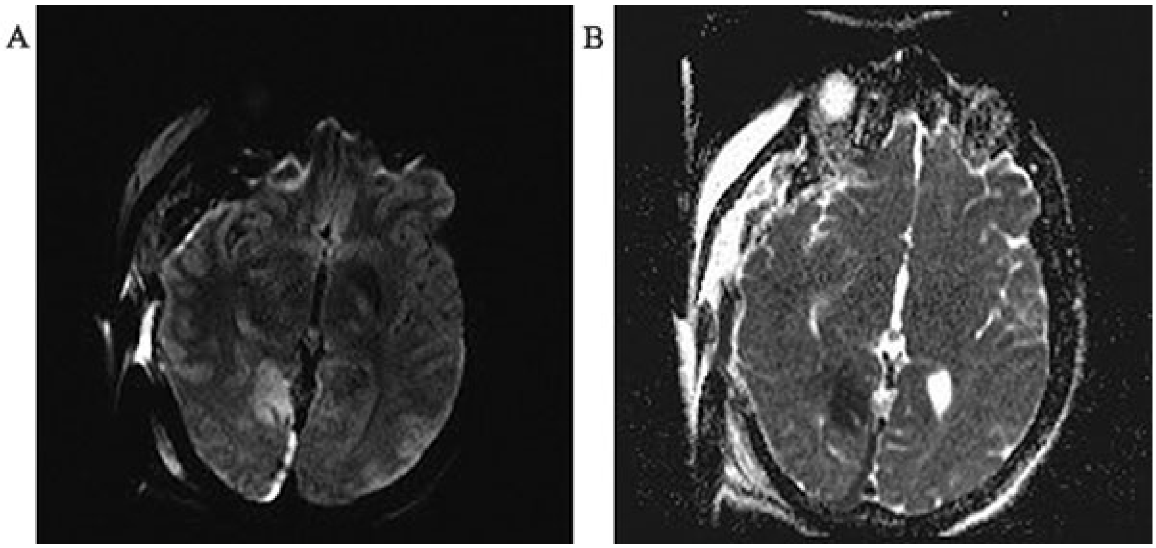


Central herniation is downward movement of the brainstem by pressure from supratentorial brain. Early findings with central herniation include cranial nerve (CN) VI palsy manifesting as lateral gaze deficits, which can be unilateral or bilateral. Like uncal herniation, if central herniation progresses, the clinical triad of a CN III palsy (including an ipsilateral nonreactive dilated pupil), coma, and posturing can occur. Occasionally, unilateral or bilateral posterior cerebral artery infarctions can occur with ongoing central or uncal herniation, due to compression of the posterior cerebral artery as it passes upward over the tentorial notch[23] (**Figure 2**).

Figure 2.

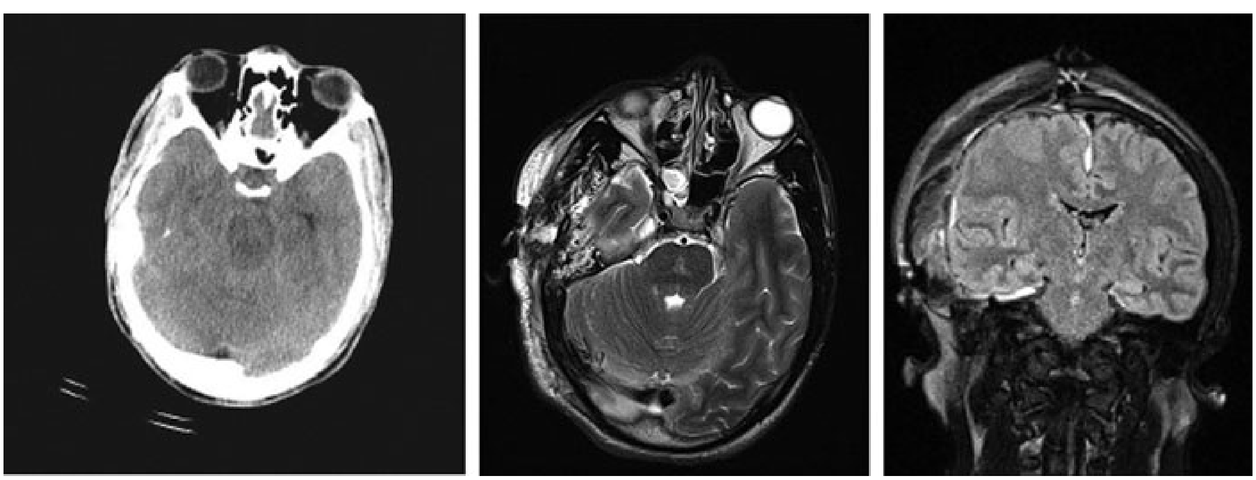
(A) Posterior cerebral artery infarcts post herniation event, diffusion-weighted imaging

(B) ADC of same patient



Uncal or *lateral transtentorial herniation* occurs when a supratentorial mass pushes the medial temporal lobe and uncus anteriorly and downward through the tentorial opening between the ipsilateral aspect of the midbrain and the tentorium. This can result in the Kernohan notch phenomenon, with hemiparesis ipsilateral to the side of the supratentorial lesion, and is a potentially false localizing sign.[22] Often, a unilaterally large pupil and ensuing third nerve palsy may herald this phenomenon. Radiographic findings of uncal herniation may be seen with resulting midbrain duret hemorrhages secondary to compromised blood flow to paramedian midbrain perforator vessels (**Figure 3**).[22] This is often an ominous radiographic finding, although it is not uniformly predictive of a poor outcome or fatality.[24]

Figure 3.



(A) Uncal herniation compressing the midbrain

(B) Axial magnetic resonance image (MRI) of same patient showing resultant Duret hemorrhages

(C) Coronal MRI of same patient

Extracranial herniation occurs when brain tissue breeches through a skull defect. Most commonly this occurs after craniectomy because the brain can shift through the surgical site. This type of herniation can occur in more than 20% of postsurgical TBI patients. Fortunately, it represents therapeutic decompression of intracranial hypertension. Untoward complications of extracranial herniation are laceration of cerebral cortex and vascular compromise of venous drainage. Making larger rather than smaller craniectomies may minimize these complications.[25]

Tonsillar herniation occurs from downward movement of the cerebellar tonsils into the foramen magnum and compression of the lower brainstem. This process can result in sudden death from compression of medullary respiratory centers and blood pressure instability. Leading causes of tonsillar herniation are posterior fossa hematomas and obstruction of CSF outflow from the fourth ventricle.[23] A posterior fossa hematoma or fourth ventricular dilation, distortion, or obliteration requires urgent neurosurgical evaluation for possible interventions, including suboccipital craniectomy.[26] Despite dramatic presentations and poor GCS scores, these patients can have good neurological outcomes. *Upward herniation* is upward movement of brain through the tentorium into the cranium. This movement can cause brainstem compression and can occur with excessive CSF drainage from an extraventricular drain. The clinical presentation of upward herniation is not well described, although as with all herniation syndromes, a decrease in mental status progressing to obtundation is common.

Paradoxical herniation, or downward herniation in the setting of an overall lowered ICP, has been reported during lumbar cistern drainage after craniectomy.[27] Few cases of this type are reported, although this can also occur in the setting of sodium dysregulation and hypernatremia (S. A. Marshall, G. S. F. Ling, personal oral communications, June 30, 2016). Remote cerebellar hemorrhages may accompany the downward herniation event. The use of a blood patch has been reported to be lifesaving when this type of herniation is due to lumbar drainage.[28]

Cerebral herniation is not necessarily a terminal event. The long-term clinical outcome of patients who have experienced a herniation event is the subject of ongoing research. Numerous reports describe patients with clinical and

radiographic herniation who have survived to discharge with variable degrees of disability.[24,28-31] Prognostic assessment of a patient who has undergone herniation is best made after the patient has had a course of aggressive medical management.

EARLY ICU MANAGEMENT

After initial emergency care, patients with moderate and severe TBI require close neurological and physiological monitoring in an ICU. Evidence demonstrates improved neurological outcomes when specialized neurological intensive care teams guide management using evidence-based clinical care.[7] The presence of other traumatic injuries may require additional care from trauma, orthopedic, craniofacial, and other specialists, and this care can be facilitated by a coordinated approach to treatment by the ICU team.

Frequent clinical neurological examinations are performed at regular intervals by well-trained providers. In the hyperacute period after TBI, examinations may be required as often as every hour but can be decreased in frequency as the patient becomes more stable and as risks for cerebral edema, hemorrhage, or vasospasm decrease. For any patient in whom intracranial hypertension is a concern, monitoring of ICP needs to be considered (discussed subsequently).

Risk of neurological worsening is highest in the first 3 to 4 days after TBI. This risk is mainly due to the development of post traumatic cerebral edema. Since the brain swells inside the rigid skull, the swelling can worsen ICP as well as lead to brain and vascular compression. Cerebral edema begins shortly after injury and peaks from 48 to 96 hours post injury.[32] Following this period, elevated ICP typically resolves and clinical improvement ensues.[33]

Ventilation and Airway Management

Ensuring adequate oxygenation and appropriate ventilation of the head-injured patient is vital. Oxygenation and ventilation goals should be to maintain adequate oxygenation with the PaO_2 60 mm Hg or greater and to avoid either chronic hypocarbia or any hypercarbia by maintaining a PCO_2 of 35 to 39 mm Hg.[8,34] Avoidance of hypoxemia or extreme hyperoxemia (PaO_2 >487 mm Hg) is an evidence-based practice as this has been shown to increase mortality and reduce the likelihood of a good outcome in at least one large clinical registry.[35] Hypoxemic episodes with PaO_2 levels lower than this are associated with worse

outcome.[36] Indications for inserting an artificial airway are a GCS score of 8 or less or clinical suspicion that the patient's ability to ventilate or protect his or her airway is currently, or will be acutely, compromised. Oral endotracheal intubation is preferred. Nasotracheal intubation is associated with potential to increase ICP.[37] Intubation and mechanical ventilation allow better control of P_{CO_2}, which if elevated can contribute to increased ICP.[8] Overly aggressive hyperventilation should be avoided given the potential for decreased cerebral perfusion at P_{CO_2} 25 mm Hg or less.[8] Use of ventilator management strategies, such as airway pressure release ventilation, aimed at improving oxygenation at the expense of ventilation, requires caution given the potential hazards of hypercapnia.[38]

Blood Pressure and Fluid Management

The objective of hemodynamic therapy in TBI is to ensure adequate brain and organ perfusion. The specific treatment goals are SBP 90 mm Hg or greater, cerebral perfusion pressure (CPP) 60 mm Hg or greater, and euvolemia. The CPP is the mean arterial pressure minus the ICP. Although not a direct measure of either global or regional cerebral blood flow, CPP indicates the overall adequacy of global brain perfusion, especially in the context of high ICP.

Blood pressure management may be challenging in head-injured patients. Patients may be in hemorrhagic shock due to accompanying injuries associated with polytrauma, and hemorrhagic shock is independently associated with poor outcome and mortality from TBI.[39-41] A SBP less than 90 mm Hg has an especially deleterious effect. When compared with hypoxemia, low SBP is less well tolerated by the brain after TBI.[42] The autoregulatory mechanisms of the neurovasculature are impaired after brain trauma, and regional cerebral blood flow may become directly dependent on systemic blood pressure, a state known as the "pressure passive" brain.[37] Experimental models show that the traumatized brain is quite susceptible to even mild ischemic states, so avoidance of even short episodes of hypotension after TBI is important.[43]

Crystalloid fluids are commonly used for resuscitation. However, for hemorrhagic shock, blood products are preferred. The clinical experience from the wars in Afghanistan and Iraq has resulted in a paradigm of blood component therapy based on red blood cells and plasma using a 1:1 ratio based on volume.[44,45] Colloid and hypotonic fluids are relatively contraindicated in TBI, as data from the Saline versus Albumin Fluid Evaluation (SAFE) study revealed

that colloid fluids containing albumin increase the risk of mortality when given to patients with brain trauma.[46] Hypotonic fluids, such as 1/2 normal saline and lactated Ringer solution, have the potential to exacerbate cerebral edema and should be avoided.[37] Maintaining euvolemia in head-injured patients is also important. In one study, TBI patients who were fluid-balance negative by 600 mL had worse outcomes.[47] The Lund concept is a controversial practice that advocates fluid restriction as a means to control cerebral edema and normalize ICP.[48] Because a hypovolemic state in TBI may compromise CPP, the Lund concept is not widely used.

Targets for CPP should be met initially with IV fluids, but if an adequate CPP cannot be maintained with IV fluids alone, vasoactive pharmacological agents may be considered. Norepinephrine and phenylephrine are preferred because they have the least effect on cerebral vasomotor tone. If vasopressors are used, continuous hemodynamic monitoring with a peripheral arterial pressure catheter is desirable, and consideration should be given to a central venous catheter.[33] Aggressive use of vasopressor agents has been associated with increased incidence of acute respiratory distress syndrome; however, this complication potentially could have been the result of targeting CPP levels of 70 mm Hg.[49] A potential benefit of the Lund concept may be attributed to the lower incidence of pulmonary complications, such as acute respiratory distress syndrome, in patients managed with more judicious fluid strategies.[50]

Intracerebral Pressure and Cerebral Edema

Elevations of ICP decrease brain perfusion and, if allowed to progress unchecked, can eventually culminate in cerebral herniation. Aggressive measures to optimize ICP should be instituted in every patient with moderate or severe TBI.

Placement of an ICP Monitor

If a brain-injured patient has a GCS score of 8 or less (after resuscitation) and an acute abnormality on CT, such as tICH, compression of the basal cisterns, evidence of contusion, or herniation, then an ICP monitor has a role in the patient's management.[8] If a patient has 2 of the following—SBP 90 mm Hg or less, motor posturing on examination, age greater than 40 years—then an ICP monitor should be placed.[8] Typically, a neurosurgeon or neurointensivist places these devices.[51,52]

Options for ICP monitoring include external ventricular drain (EVD), intraparenchymal fiberoptic monitor, subdural bolt, and epidural fiberoptic catheters. The EVD provides the most accurate measurement of ICP but is also the most invasive to place. After a "burr hole" is made in the cranium, the catheter is passed through brain parenchyma into lateral ventricle, with the tip of the catheter ideally resting in the third ventricle, which is near the center of the cranial vault. The EVD is the most reliable device and can be zeroed after insertion. Furthermore, it can be used to drain CSF and thus provides a therapeutic option. Other devices, such as the fiberoptic monitor, are less invasive as they require minimal or no penetration of brain parenchyma. As closed systems, they carry a lower incidence of infection but, unfortunately, are subject to measurement drift and cannot be zeroed externally once placed. Unlike the EVD, these devices do not provide a therapeutic option because CSF cannot be drained. Only the EVD provides both a measure of and a treatment for elevated ICP. If hydrocephalus is seen on imaging, an EVD is indisputably the best option.

Other monitoring devices such as brain tissue oxygenation monitors, microdialysis catheters, and jugular venous saturation monitors can be used to tailor therapy, but insufficient evidence of their clinical efficacy is available to support endorsement for routine use.[8] Like most medical devices, monitoring devices have potential untoward effects. Brain tissue oxygen monitors have been reported to be associated with increased fluid and vasopressor use and the subsequent development of pulmonary complications as well as intractable elevated ICP in patients with TBI.[50] These and other devices are the subject of a number of ongoing clinical trials.[53]

Treatment Goals

The clinical goal for ICP is to maintain normal pressure, which is 15 mm Hg or less or 20 cm H_2O. Elevations in ICP greater than 25 mm Hg are associated with poor outcome, and thus interventions should be aimed at reducing ICP to less than this level with a goal ICP of 20 cm H_2O. More specifically, current guidelines specify instituting measures to control ICP when pressures of 20 mm Hg are reached, and aggressive means are recommended to prevent ICP elevations greater than 25 mm Hg.[8] This approach must be balanced with the goal of maintaining CPP, as some interventions to decrease ICP, such as mannitol, may also have hypotensive hemodynamic effects.

Hyperosmolar Therapy of Elevated ICP

An important management approach to elevated ICP involves pharmacological creation of an osmotic gradient between brain and blood, which causes movement of water from intracellular and extracellular compartments of the brain into the vasculature, thus reducing the volume of the overall cranial compartment.[54] One approach is to administer a large solute such as mannitol. Another approach takes advantage of the large contribution of serum osmolality made by sodium. This is done by IV administration of fluids with a high sodium concentration, such as HTS.

Mannitol

A mainstay of therapy for intracranial hypertension for many years, mannitol can be given intravenously via a peripheral or central IV line at a dose of 0.25 to 1.0 g/kg. Small doses of mannitol (0.25 g/kg) have been shown to effectively reduce ICP in patients with TBI, but the effects of mannitol may not last as long as when given at higher doses.[55] Mannitol administration results in decreased ICP and improvements in cerebral blood flow and CPP.[56] Past recommendations for mannitol to be given as bolus rather than continuous infusions are no longer supported, but bolus dosing is still most widely used.[8] Additional doses of mannitol should be guided by close monitoring of serum osmolality. A serum osmolality of 320 mOsm/L is generally accepted as treatment end point; some investigators advocate targeting slightly higher levels but caution that renal dysfunction and other complications are more likely to occur at higher levels of osmolality.[57]

Hypertonic Saline

An equally important option for hyperosmolar therapy is HTS. Studies using 7.5% and 23.4% HTS have demonstrated efficacy. Recent evidence supports the use of bolus doses of 30 to 60 mL of 23.4% HTS to emergently reverse a cerebral herniation event.[29] An additional benefit of using 23.4% HTS is that its ameliorative effect on ICP lasts longer than that of mannitol.[58] When used, 23.4% HTS must be administered via a central venous line over 10 to 15 minutes to prevent phlebitis and hypotension. A commonly used initial treatment goal is to achieve a serum sodium level of 145 to 155 mEq/L, which is equivalent to a serum osmolality of 300 to 320 mOsm/L in most patients.[54] Recent evidence shows that 23.4% HTS can reduce ICP by a mean value of 8.3 mm Hg when given for ICP less than 20 mm Hg and can increase CPP values by 6 mm Hg

when pretreatment CPP values are less than 70 mm Hg.[59] A continuous IV infusion of 2% or 3% HTS can maintain high serum osmolality while also functioning as a volume expander. The development of hyperchloremic metabolic acidosis from prolonged infusions of 2% or 3% saline may be lessened by the use of a 50:50 mix of sodium chloride and sodium acetate. A 2% concentration of HTS can be given through a peripheral IV catheter, but at 3% or higher, HTS must be given via a central line due to its potential to cause phlebitis. The infusion rate is set based on the patient's intravascular requirements and desired serum sodium level. Large (100-250 mL) IV bolus doses can be given to treat episodes of intracranial hypertension or as a volume expander to treat systemic hypotension.

If continuous infusions of hyperosmolar solutions are used, serum sodium should be monitored at least every 6 hours. Rapid decreases in serum sodium should be avoided in order to prevent rebound cerebral edema.[54] To avoid the feared complication of central pontine myelinolysis, the clinician must take care when increasing serum sodium levels in patients with chronic hyponatremic states, but the risk of central pontine myelinolysis is very low if the patient is initially normonatremic. Dehydration and volume depletion likewise must be avoided.[47] In clinical practice, HTS therapy is maintained for the first several days after injury, and after the period of peak edema elapses (typically 4-5 days after injury), HTS infusions can be scaled back to normal saline, targeting a return to a normonatremic state.

Reducing Intracranial Volume for Treatment of Elevated ICP

Because the brain is encased in the skull, there is a direct relationship between the volume and pressure within the cranial vault. This constitutes the Monro-Kellie doctrine. To reduce pressure, volume needs to be removed. This volume can come from any of the 3 constitutive intracranial components—blood, CSF, and brain—or from abnormal components, such as hematoma or tumor.

Head Positioning

Simple interventions include keeping the head of the bed at 30° and maintaining the patient's head midline, avoiding any circumferential neck dressings, and avoiding placement of central venous catheters in the dominant internal jugular vein. All of these considerations optimize venous outflow from the head, which reduces intracranial blood volume. Patients should not be placed in the Trendelenburg position for central catheter placement if they have increased ICP,

because this leads to venous congestion causing cerebral blood volume to increase, which risks brain herniation.[54]

Hyperventilation

Hyperventilation reliably lowers ICP acutely but should be used only as a temporary emergency intervention for acute elevations in ICP. Prolonged hyperventilation has been clearly associated with exacerbation of cerebral ischemia.[60] Short periods of hyperventilation are acceptable as a temporizing measure until other (surgical, hyperosmolar, metabolic) means of managing increased ICP are instituted. The reduction in P_{CO_2} leads to decreased cerebral blood flow and thus decreased cerebral blood volume. Excessive hyperventilation (P_{CO_2} <25 mm Hg) poses a significant risk of worsening ischemia in compromised brain regions. Furthermore, if hyperventilation is continued for longer than 6-12 hours, metabolic compensation begins to negate the effects of the respiratory alkalosis. The recommended goal for a chronic P_{CO_2} is normocapnea (40 mm Hg), but during an impending herniation event, hyperventilation will acutely and reliably lower P_{CO_2}, as well as ICP, within seconds. Current recommendations strongly advocate avoiding sustained levels below 25 mm Hg.[8,37]

Cerebrospinal Fluid Drainage

If an EVD has been placed during the acute phase of management and the ICP is found to be elevated, then the CSF drainage valve (“pop-off”) may be placed at 0 mm Hg to allow continuous drainage of CSF. Once the patient tolerates this, the pop-off level may be increased, typically in increments of 5 mm Hg per day. Intolerance is characterized by elevation of ICP to greater than 25 mm Hg and/or neurological deterioration. If either occurs, the pop-off needs to be lowered again. During drainage, the EVD cannot measure ICP. Thus, at frequent intervals, the EVD drain valve must be shut off (clamped) in order to measure the ICP. Once a patient tolerates the valve being set at 20 mm Hg for at least 24 hours, a trial of ICP measurement only (clamping) may be attempted with the intent of removing the EVD. Alternative approaches to using the EVD are available, such as keeping the pop-off at 10 mm Hg to allow drainage whenever ICP goes above this level. However, all methods capitalize on the ability to drain CSF as a means of reducing intracranial CSF volume, and thus overall intracranial volume, to reduce ICP.

Agents to Decrease the Metabolic Activity of the Brain

If ICP remains poorly controlled despite all of the efforts described above, then induced pharmacological coma may be considered. The proposed mechanism by which pharmacological coma lowers ICP is through reduction of cerebral metabolism, measured by the cerebral metabolic rate of oxygen, with concomitant reductions in cerebral blood flow and reduced cerebral tissue oxygen demand. The most common agent used for pharmacological coma is pentobarbital. This drug can be administered intravenously at a loading dose of 5 mg/kg, followed by an infusion of 1 to 3 mg/kg/h. A "high-dose" regimen begins with an IV loading dose of 10 mg/kg over 30 minutes followed by a 5 mg/kg/h infusion for 3 hours, followed by 1 mg/kg/h titrated to therapeutic goals, which are either burst suppression on continuous electroencephalography (EEG) monitoring or reduction in ICP.[47] If burst suppression is not obtained with this dose, then another smaller bolus loading dose and increased rate can be given until a satisfactory EEG tracing is seen or ICP is controlled. Additional loading doses must be part of any increase in barbiturate therapy, because merely increasing the continuous infusion rate without a bolus will not affect ICP, EEG results, or serum levels of pentobarbital for some time. Other barbiturates may be used, including the much shorter acting thiopental, whose half-life of 5 hours is suited for short-term therapy of elevations in ICP.[54] Thiopental doses of 200 to 500 mg can be given via IV bolus, but the patient must undergo close monitoring for hypotension. Use of medications of this class are reserved for patients with an established airway. Recent geopolitical tensions have severely limited the domestic supply and availability of thiopental because of its off-label use in the United States by state corrections institutions as part of lethal injection procedures.[61]

Another option for pharmacological coma is propofol, which is given at an IV loading dose of 2 mg/kg, followed by a titrated infusion of up to 100 to 150 μg/kg/min. The use of propofol for this clinical indication is controversial. In terms of efficacy, a study using propofol for ICP reduction showed a failure of an improvement in 6-month outcome.[62] Long-term and high-dose propofol infusions have been associated with the development of propofol infusion syndrome, which consists of renal failure, rhabdomyolysis, hyperkalemia, myocardial failure, metabolic acidosis, and death. The mechanism for this is not fully understood, but significant caution must be used in administering any infusion greater than 5 mg/kg/h, particularly for treatment lasting longer than 48 hours.[8] If propofol or barbiturates are used, then continuous EEG monitoring

should be performed as the therapeutic goal will be either burst-suppression on EEG or desired degree of ICP control.

Targeted Temperature Management

Induced hypothermia for TBI is a potential therapy undergoing study but has not been conclusively shown to be beneficial for improving clinical outcome. In preclinical models, induced hypothermia is one of the most effective TBI therapies.[63] However, clinical trials conducted to date have shown modest to no clinical improvement. The most recent trial, Eurotherm3235, showed no benefit of induced hypothermia (32°C-35°C) following TBI with increased ICP (>20 mm Hg).[64] Some clinicians use prophylactic hypothermia to decrease the risk of elevated ICP in severe TBI as a second-tier therapy. If induced hypothermia is used, modalities of induction include skin-applied gel cooling systems, air-circulating cooling blankets, surface ice packing, iced gastric lavage, and IV methods.[54] The potential side-effects of induced hypothermia include coagulopathic and antiplatelet effects, especially in the setting of hemorrhagic TBI.[65-69]

Normothermia

Maintaining normothermia and avoiding hyperthermia in TBI patients are strongly recommended.[70]

APPROACH TO AN ICP EMERGENCY

When ICP elevation becomes an emergency or lasts persistently beyond recommended levels, a change in the neurological examination is manifest, or a herniation event occurs, a brain code should be initiated. This term *brain code* has gained popularity, and many believe that a codified approach to a herniation event or other acute elevations in ICP is best managed via a treatment algorithm similar to an ACLS protocol. This may encourage intensivists that do not routinely work in the neurosciences to develop a standardized approach to such emergencies.[30] To reiterate, the brain code consists of elevating the head of the bed to 30° with the patient's head midline, using acute hyperventilation to a PCO_2 to 30-35, administering mannitol (0.25-1.0 g/kg IV), and considering 23.4% HTS (30-60 mL IV through a central venous catheter).

Sample Approach

One approach entails beginning initial treatment of elevated ICP with confirmation that the waveform and ICP reading is accurate. Seizure activity must be ruled out if suspected. Brain CT imaging should be considered for any unexpected increase in ICP without explanation. Maneuvers such as clearing the endotracheal tube of obstruction, repositioning the patient's head to midline, sitting the patient up at 30°, establishing normothermia, and eliminating suctioning or other noxious stimuli may help lower temporary spikes in ICP. If these strategies are unsuccessful and the ICP reading is believed to be accurate, a brief period of hyperventilation may be performed. Blood gas data or end-tidal CO_2 analysis may ensure the absence of hypercapnea. Sodium level should be checked and treated if low. If central access is available, then 30 mL of 23.4% HTS may be given via a central line over 10 to 15 minutes. This can be done faster, but augmentation of CPP with agents such as phenylephrine may be required to maintain perfusion (S. A. Marshall, G. S. F. Ling, personal oral communications, June 30, 2016). Alternatively, mannitol or bolus doses of 3% saline may be given. The dose of mannitol chosen depends on the clinical situation. If a herniation event is strongly suspected, then 1 g/kg is given. If a less dire clinical situation is manifest, then lower doses such as 0.25 to 0.5 g/kg may be used. In a herniation event, central access should be readied, and clinicians should consider placing a temporary femoral central venous catheter to avoid the necessity of Trendelenburg positioning.[54] In a patient with moderate or severe TBI and concerns for elevated ICP, it is reasonable to obtain central venous access early, in either the subclavian or femoral veins.

If ICP continues to be elevated after these maneuvers, then additional HTS can be given as well as further doses of mannitol, targeting a serum osmolality of 320 to 340 mOsm/L. Standing infusions of HTS such as 3% can be started or increased, with goal sodium values that may exceed 160 mEq/L. Further medical management may include the use of propofol, thiopental, and possibly pharmacological coma and/or hemicraniectomy.

SURGICAL TREATMENT OF CEREBRAL EDEMA

Conventional management reserves surgical decompression and craniectomy for patients with very severe TBI or those in whom medical management alone is insufficient.

Decompressive Craniectomy

Decompressive craniectomy (DC) is a neurosurgical intervention that is an optional consideration for managing intractable elevations in ICP. The clinical evidence supporting the use of DC to improve neurological outcome is lacking.

The Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial showed that DC resulted in better ICP control and other metrics of better overall management of brain injury, including length of stay, but was associated with a worse long-term neurological outcome.[71] Reserving DC as an option for ICP management has practical use. For example, the US military uses DC for managing patients who are at high risk for elevations in ICP and will be undergoing long intercontinental medical evacuation flights.[72] Under these circumstances, DC is performed very early, often within a few hours after injury.

Seizure Prophylaxis

Patients with TBI are at risk for both early (≤7 days) and late (>7 days) posttraumatic seizures. This risk may be worsened by tICH. A seizure in the acute injury phase can exacerbate the injury. The current recommendations are to provide an antiepileptic drug (AED) for the first 7 days after TBI and then discontinue. Phenytoin, carbamazepine, phenobarbital, and valproate have all been shown to be beneficial in reducing the risk of early posttraumatic seizures.[73,74] No AED has been shown to prevent the development of late posttraumatic seizures. This is unfortunate, because TBI patients are at risk for development of late posttraumatic seizures. Studies have shown that when followed for 15 years after TBI, approximately 50% of patients will develop late posttraumatic seizures. Clearly, a large percentage of these patients will however remain free of any seizure activity, so the recommended approach following TBI is to stop AED therapy after the first 7 days and only reinstitute treatment should late seizures occur.[8] Additionally, the potential for cognitive and other side effects of phenytoin makes prolonged prophylactic use of this medication less attractive.[75] If a patient requires IV medications, alternatives to phenytoin and fosphenytoin are valproate and levetiracetam. Levetiracetam has shown to be highly effective in preclinical TBI models, although a rigorous human clinical TBI trial has not been conducted.[76]

Little evidence is available to support or refute use of AEDs for prevention of seizures related to penetrating TBI. Because the risk of seizure following penetrating TBI is much higher than that following nonpenetrating closed-head TBI, in practice, AEDs are universally prescribed by many providers using the guidelines established for nonpenetrating TBI.[20,77]

Steroids

Steroids should not be used for improving neurological outcome following TBI. This is supported by Class 1 evidence. The effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH) demonstrated that methylprednisolone did not improve neurological outcome but was associated with increased risk of death and disability.[78]

Transfusion Threshold

Patients with TBI are at risk of cerebral ischemia from cerebral edema and vasospasm. The current guidelines recommend a hematocrit (HCT) goal of 28% or higher. A recent study showed that a transfusion threshold of hemoglobin 7 g/dL is better than 10 g/dL.[79] No difference in neurological outcome was found between the 2 thresholds, but the lower transfusion threshold was associated with less adverse effects. This provides new evidence supporting a lower HCT goal.

Prevention of Deep Venous Thrombosis

An important consideration is prevention of venous thromboembolism (VTE). Clinicians must balance the concern for VTE against the potential for worsening intracranial bleeding with use of anticoagulants. Patients with TBI are at high risk for developing deep venous thrombosis (DVT) with subsequent VTE because they are often immobile during the acute phase of their care and often have persistent extremity paresis or plegia. The optimal approach for VTE and DVT prophylaxis in TBI, or in TBI complicated by intracranial hemorrhage (SDH, traumatic subarachnoid hemorrhage, tICH) is unclear. Both sequential compression devices and anticoagulation therapy are recommended. Sequential compression devices used on the lower extremities are minimally invasive and are not associated with worsening intracranial hemorrhage, and they should be placed as soon as possible if no contraindications exist (such as compartment syndrome). The optimal timing of introduction of unfractionated or low-molecular-weight heparin in TBI patients is uncertain. If no other contraindications to heparin use are present, treatment should be started within the first 36 hours after TBI.[78] The routine placement of inferior vena cava filters is controversial, and placement is currently supported only by a low-level recommendation in patients with a GCS score less than 8 and contraindications to anticoagulation.[80,81]

REVIEW OF GUIDELINES

The key goals for managing moderate to severe TBI are ICP less than 25 mm Hg, CPP greater than 60 mm Hg, SBP greater than 90 mm Hg, PO_2 greater than 60 mm Hg or oxygen saturation greater than 90%, head of bed elevation 30°, PCO_2 30-35 mm Hg if hyperventilating for herniation, use of hypertonic resuscitation fluids (normal saline or higher), HCT greater than 28, artificial airway for GCS score of 8 or less, maintenance of normothermia, avoidance of steroids, and use of AEDs for only 7 days (begin within 24 hours) after injury.

SUMMARY

The critical care management of TBI has advanced over the past few decades, resulting in a significant improvement in patient outcome. This success is attributable to a disciplined, evidence-based approach to this injury and highly coordinated efforts of medical, surgical, nursing, and allied therapy professionals specializing in the care of neurological injuries. The prehospital and in-hospital care of TBI is predominantly concerned with minimizing secondary injury from TBI in order to optimize neurological and functional recovery. Maintaining brain perfusion, controlling ICP, and preventing morbidity associated with critical illness are paramount. As new surgical, pharmacological, and medical approaches are introduced, clinicians will have increasing opportunity to better manage these patients and enhance their long-term outcomes with the hope of returning them to their premorbid level of function.

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CHAPTER 4

Neurological Criteria for Death in Adults

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Key words: brain death, apnea test, coma, organ donation after neurological death, organ donation after cardiac death

DETERMINATION OF DEATH BY NEUROLOGIC CRITERIA IN ADULTS

Definition of Death

The Uniform Determination of Death Act (UDDA) states, "An individual who has sustained either 1) irreversible cessation of circulatory and respiratory functions, or 2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made with accepted medical standards."[1]

Using the definition by the UDDA, the American Academy of Neurology (AAN) practice parameters[2] suggest that determination of "cessation of all functions of the entire brain, including the brain stem" should include the following:

1. Presence of unresponsive coma
2. Absence of brainstem reflexes
3. Absence of respiratory drive after a carbon dioxide challenge

To ensure that the cessation of brain function is irreversible, the cause of coma must be known and must be consistent with permanent cessation of brain function. Conditions that may mimic a brain-death examination without cessation of brain function must be ruled out.

Legal and Ethical Considerations

Practice varies considerably between countries, states, and different hospitals in terms of what are "accepted medical standards" in the determination of brain death. Each country, and each state in the United States of America, has its own legal regulations for death by brain criteria.[3] Healthcare providers should familiarize themselves with local regulations and protocols of brain death determination. There are even religious exemptions within the United States.

Clinical History

The first step toward considering determination of death by brain criteria is to determine whether the diagnosis and pathophysiological state are consistent with an irreversible injury to the brain that can lead to loss of total brain function. Definite clinical or neuroimaging evidence of an acute central nervous system catastrophe compatible with brain death must be present before such determination can proceed. Some of the leading causes of brain death in the United States include severe traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, large strokes with brain swelling and herniation, cerebral edema from fulminant hepatic failure, and hypoxic ischemic brain injury from cardiac arrest.[4]

Exclusion of Complicating Conditions

Several important medical conditions may confound the clinical neurological examination and should be excluded prior to determination of brain death. These conditions include severe electrolyte disturbances, acidosis, hypothermia,[5] endocrine abnormalities such as hypothyroidism and myxedema coma, drug intoxication, and severe liver or renal failure. No national recommendations are available regarding specific threshold values for these metabolic disturbances other than a core temperature of 36°C (96.8°F) or higher.[2] In 2010, the AAN recommended a set of criteria that must be met prior to clinical examination for determination of brain death (**Table 1**).

Table 1. Prerequisites for Determination of Brain Death

Coma, irreversible and cause known
Neuroimaging explains coma
Absence of any drug exposures that may cause central nervous system depression (toxicology screen if indicated; serum barbiturate level <10 μg/mL)

No evidence of residual paralytics (electrical stimulation if paralytics used)
Absence of severe acid-base, electrolyte, endocrine abnormality
Normothermia or mild hypothermia (core temperature >36°C [96.8°F])
Systolic blood pressure ≥100 mm Hg
No spontaneous respirations

Medications such as benzodiazepines, barbiturates, and narcotics can suppress neurological function and confound neurological examination in the determination of irreversible coma. A careful history is necessary to determine whether the patient has been exposed to medications that can potentially confound examination. Serum and urine toxicology screen can be used to determine whether such exposures occurred. No consensus is available regarding the threshold drug level below which the examination is not confounded. Should the patient have such an exposure, general recommendations suggest waiting for a time period equivalent to 4 to 7 times the half-lives of the drugs of concern before performing clinical examination for brain death determination. In patients with renal or hepatic failure or in patients treated with therapeutic hypothermia, this interval should be extended.

Prolonged effects of neuromuscular blockade can confound examination. When a patient has received neuromuscular blocking medications, it is highly recommended to use a peripheral nerve stimulator to objectively confirm the resolution of medication effect before proceeding with brain death determination. Of note, hypothermia significantly delays clearance of neuromuscular blocking agents. Therefore, residual effects of paralytic medications must be actively ruled out in patients exposed to either accidental or therapeutic hypothermia.

Clinical Examination

The AAN published original practice parameters for determination of brain death in adults in 1995[6] and updated guidelines in 2010. No patients who fulfill the clinical criteria of brain death per AAN practice guidelines have recovered brain function.[2]

Brain death determination is a clinical diagnosis based on plausible history of

catastrophic and irreversible brain injury and a clinical examination consistent with complete loss of brainstem function, including an apnea test. Ancillary tests are used only if a patient's condition prohibits adequate assessment of clinical examination.

Key components of clinical examination consistent with brain death are the following:

1. Confirm persistent coma.
2. Confirm the absence of all brainstem reflexes.
3. Confirm the absence of motor response to noxious stimuli in all limbs.
4. Confirm apnea (lack of respiratory drive).

Table 2 lists key components of bedside neurological examination, recommended techniques, and features that are consistent with brain death.

Table 2. Key Components of Neurological Examination in the Determination of Brain Death

Examination	Localization	Technique	Finding Consistent With Brain Death
Response to noxious stimuli	Cerebral cortex, thalami, and brainstem	Observe motor response or grimace to stimuli such as sternal rub, nasal tickle, and supraorbital or nail-bed pressure.	No motor response or grimace to noxious stimuli Spinal reflexes and motor movements acceptable[a]
Pupillary light response	Cranial nerve II; brainstem	Shine focused and sustained, bright light into each pupil.	Fixed and dilated pupils with no response to light
Corneal reflex	Cranial nerves V and VII; brainstem	Stimulate the cornea (not conjunctiva) with cotton swab or gauze and look for reflexive eye blink.	No corneal response on either side
Cough reflex	Cranial nerves IX	Stimulate the larynx with cotton swab or suction device; insert suction catheter through	No cough response to

	and X; brainstem	endotracheal tube.	laryngeal or bronchial stimulation
Gag reflex	Cranial nerves IX and X; brainstem	Stimulate the posterior pharynx with a cotton swab or suction device.	No gag response to pharyngeal stimulation bilaterally
Oculocephalic reflex	Cranial nerves III, IV, VI, and VII/VIII; brainstem	Rapidly turn the patient's head from midline to one and then the other side, and observe lateral movement of eyes contralateral to the direction of head turn. Vertical movements of eyes can similarly be tested with rapid extension and flexion of the neck.	No movement of eyes with head turn and with neck flexion-extension
Oculovestibular (cold-calorics) test	Cranial nerves III, IV, VI, and VII/VIII; brainstem	Elevate the patient's head to 30°. Perform otoscopic examination to exclude rupture of the tympanic membrane prior to this test. Irrigate each tympanic membrane with 50 mL of ice water via a small catheter inserted into the external auditory canal. Observe tonic eye deviation toward the side of ice water irrigation. Wait 5-10 min before stimulating the opposite tympanum.	No eye movement to injection of ice water
Motor response to noxious stimuli	Complete motor and sensory tracts	Provide sustained noxious stimuli to each limb separately and observe for movement in that limb or any other limb.	No spontaneous movement No withdrawal to noxious stimuli No extensor or flexor posturing Spinal reflexes allowed[a]

[a]See the section Potential Pitfalls in Clinical Determination of Brain Death.

Observation Period

Insufficient data are available to determine the utility of serial neurological examinations or the adequate observation period to ensure cessation of all brain

function. Practice varies widely throughout the United States and the world. In general, most centers require a minimum of 2 clinical examinations consistent with brain death separated by a certain time interval before death by brain criteria can be declared.[3]

One special population to consider is post–cardiac arrest patients treated with therapeutic hypothermia. The duration of the effects of hypothermia on the accuracy of neurological examination is unknown. No guidelines are available regarding how long to wait before proceeding with brain death determination in this population. An important note of caution is raised by a case report of a patient who met all brain death criteria as recommended by the AAN and who subsequently had transient return of brainstem function including spontaneous respirations 24 hours after pronouncement of brain death[7]; this case argues for an observation period of 24 hours or longer after body temperature returns to 36°C (96.8°F) or higher before proceeding with clinical determination of death by brain criteria.

Apnea Testing

Loss of brainstem function ultimately produces loss of breathing, which is an important component in determination of brain death. Brainstem respiratory control depends on centrally located chemoreceptors that sense changes in P_{CO_2} and pH of the cerebrospinal fluid, which reflect changes in the plasma P_{CO_2}. It is not known what arterial P_{CO_2} produces maximal stimulation of these chemoreceptors in the brainstem. Using available data from case series,[8] the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research reported that an arterial P_{CO_2} level of 60 mm Hg or greater produces maximal stimulation of the brainstem, and this is the threshold level recommended for apnea testing by the current AAN practice guidelines.

Apnea testing should be performed as the last step in determining clinical brain death, after establishment of a diagnosis consistent with central nervous system catastrophe and a clinical examination consistent with complete absence of brainstem reflexes and motor function in the absence of confounding drug effect or metabolic derangements.

Sample Guideline for Apnea Test

Various techniques are used in performing the apnea test, and no data are

available to suggest the comparative safety of these techniques.[9] Healthcare providers should consult their institutional protocol for local guidelines and requirements.

The apnea test generally can be performed without complications or danger of cardiopulmonary death for the patient. However, potential complications of the apnea test can include pneumothorax and cardiac arrest. Clinical conditions such as severe hemodynamic instability, requirement for high positive end-expiratory pressure, or refractory hypoxemia despite preoxygenation may make it impossible to begin an apnea test or may result in termination of the apnea test before it is completed.[10]

Adequate preparation for apnea testing may decrease the rate of terminated examinations due to hemodynamic or other complications. Prior to initiation of apnea, patients can be preoxygenated on 100% FIO_2 for at least 10 minutes and reach arterial PaO_2 higher than 200 mm Hg. Patients should have a core temperature higher than 36.5°C (97.7°F)[4] and adequate perfusion pressure (systolic blood pressure ≥100 mm Hg). Arterial PCO_2 should be within a normal range (35-45 mm Hg).

The most common side effects of hypercarbia and respiratory acidosis during apnea testing are hypotension and cardiac arrhythmias such as frequent premature ventricular contractions or ventricular tachycardia. Pretest normalization of electrolytes and pH and maintenance of adequate oxygenation may reduce the incidence of severe cardiac arrhythmia during apnea. Oxygenation during apnea may be sustained by delivering high-flow oxygen via a catheter placed at the level of the carina or by using a T-piece with a continuous positive airway pressure valve that delivers high-flow oxygen throughout the duration of apnea test. Vasopressors can be used to maintain adequate perfusion pressure during apnea testing.[11] Apnea testing should be performed with continuous electrocardiographic and blood oxygen monitoring as well as frequent (eg, every 3-5 minutes) blood pressure measurements.

Immediately prior to initiation of apnea, an arterial gas blood sample should be analyzed to determine starting arterial PCO_2. It is generally recommended that the patient be disconnected from the ventilator circuit during apnea testing so as to avoid detection of false-positive respiratory efforts by the ventilator. After initiation of apnea, the patient is observed closely for any evidence of respiratory movements. Respiration is defined as abdominal or chest excursions that produce tidal volumes.[4] If the patient has clinical evidence of respiration, the

apnea test should be terminated, as the results are inconsistent with complete loss of brainstem function. If the patient does not manifest clinical evidence of respiratory efforts, the apnea period can be continued up to 10 minutes if hemodynamic stability can be maintained. Repeat arterial blood gas samples can be collected at 8 and then at 10 minutes of apnea for evaluation of arterial P_{CO_2} increase. The apnea test confirms complete absence of brainstem function and is consistent with brain death if the patient has no respiratory efforts for more than 8 minutes and has a final arterial P_{CO_2} of 60 mm Hg or higher or has an increase of P_{CO_2} by more than 20 mm Hg at the end of the apnea test.

A patient may develop significant cardiac arrhythmia, hypoxia, or refractory hypotension that results in termination of the apnea test before reaching the 8- to 10-minute period of apnea. If this occurs, an arterial blood gas sample should be drawn immediately prior to aborting the apnea test. If the P_{CO_2} rises above 60 mm Hg or increases by more than 20 mm Hg with less than 8 minutes of apnea, the test results are still consistent with complete absence of brainstem function and brain death. If the P_{CO_2} does not rise above 60 mm Hg and the apnea test has to be stopped due to clinical instability, performance of an ancillary test to confirm the diagnosis of brain death is appropriate.

Potential Pitfalls in Clinical Determination of Brain Death

Definition of Coma

Coma is a necessary but not sufficient criterion for brain death. Neurological definition of coma requires that the patient be unconscious with no arousal or eye opening to stimulation.[12] It is important to distinguish coma from other pathological states such as persistent vegetative state, where the patient is awake with preserved sleep-wake cycles but lacks awareness. Patients in persistent vegetative state do not meet criteria for brain death.

Examination Mimics

Reports of conditions mimicking brain death include fulminant Guillain-Barré syndrome, organophosphate intoxication, high cervical spinal cord injury, lidocaine toxicity, baclofen overdose, and delayed vecuronium clearance.[2] Careful examination found that none of these cases fulfill all criteria for brain death determination put forth by the 1995 AAN practice parameters. It is important to recognize and rule out potential examination mimics prior to brain

death determination.

Motor Movements Consistent With Brain Death

Spontaneous and reflexive complex motor movements can be seen in patients with cessation of all brain function. These movements are mediated through the spinal cord or are spontaneous muscle movements due to afferent denervation. Such reported movements include facial myokymia, transient bilateral finger tremor, repetitive leg movements, retained plantar reflexes, vermicular twitching resembling muscle fasciculations, ocular microtremor, and cyclical constriction and dilatation of light-fixed pupils often referred to as "hippus."[13] Differentiation between spinal-mediated movements and motor responses mediated through brain activity can be challenging and requires a trained examiner.

In rare occasions, dramatic movements of spinal origin can be observed in brain death. These movements may occur spontaneously or in response to stimulations such as a mechanical breath from the ventilator. These movements can include rapid flexion of arms, raising of all limbs off the bed, grasping movements, spontaneous jerking of one leg, walking-like movements, and movements of the arms up to the point of reaching the endotracheal tube, often called the "Lazarus sign."[14] If present, these movements are stereotypical, and careful examination can distinguish them from other movements that represent presence of brain function. However, the presence of these movements can be disturbing to the healthcare team and particularly to family members, and these movements have been mistaken as a miraculous event.[14] Careful family counseling is important in these situations.

Persistent spinal-mediated reflexes are consistent with the diagnosis of brain death. These include muscle stretch reflexes in the limbs, superficial abdominal reflexes, and Babinski reflexes.

Pitfalls of Pupillary and Eye Movement Examinations

Topical use of drugs in the eye and trauma to the cornea or bulbus oculi may cause absence of pupillary light reflex that is not indicative of central nervous system condition. These factors should be carefully excluded prior to pupillary examination.

Similarly, numerous medication toxicities can diminish or abolish the caloric response of eye movements regardless of brain function. These medications

include sedatives, aminoglycosides, tricyclic antidepressants, anticholinergic medications, anticonvulsants, and chemotherapeutic agents. Furthermore, facial or ocular trauma may result in restricted movement of the globes due to fracture and hematoma formation regardless of brain function. Trauma and drug intoxications may also reduce corneal reflexes. These factors must be carefully excluded prior to the examination of eye movements.

False-Positive Respiratory Efforts

Ventilators may sense small changes in tubing pressure, such as changes in transpleural pressure from the heartbeat, and provide a breath. This may be erroneously interpreted as breathing effort by the patient during apnea testing.[15,16] Such an error can be avoided by performing apnea testing without connecting to a ventilator circuit.

Some brain-dead patients manifest respiratory-like movements that are reflexive and are consistent with brain death. Such movements may include shoulder elevation and adduction, back arching, and intercostal expansion. These movements can be distinguished from true respirations because they are never associated with significant tidal volumes.

Patients With Abnormal Carbon Dioxide Response

The $P\text{CO}_2$ level that represents maximal brainstem stimulation may be very different in patients with chronic hypercapnia or severe sleep apnea. Confirmatory tests can be helpful in determination of brain death in these patients.

Patients Receiving Extracorporeal Membrane Oxygenation

The use of extracorporeal membrane oxygenation (ECMO) in resuscitation presents new challenges to the traditional methods used to determine brain death, particularly with regard to apnea testing. No guidelines or consensus is available regarding methods for determination of brain death while a patient is receiving ECMO. Small case series have described a variety of techniques, including targeting a mean arterial pressure of 75 to 80 mm Hg rather than a systolic blood pressure of 100 mm Hg, preoxygenation by increasing $F\text{IO}_2$ in the ECMO circuit followed by decreasing sweep gas flow rate to minimize carbon dioxide removal, and increasing the duration of apnea test to allow sufficient carbon dioxide accumulation.[17,18] Practitioners should consult their local institutional

policies and guidelines for determination of clinical brain death in this patient population.

Other Signs and Symptoms Consistent With Brain Death

Absence of hypotension or diabetes insipidus can be consistent with brain death. Brain-dead patients can develop intermittent hypertension, as well as sweating, blushing, and tachycardia. These observations do not exclude the diagnosis of brain death.

Ancillary Laboratory Tests

Brain death is a clinical diagnosis. A confirmatory ancillary laboratory test is needed when specific components of clinical determination of brain death cannot be evaluated in a patient. Many of the ancillary confirmatory tests evaluate cessation of intracranial blood flow as a means to determine brain death. Therefore, patients should have adequate perfusion pressure to be eligible for brain death determination with such studies. Other tests such as electroencephalography (EEG) evaluate evidence of neuronal activities and can be confounded by medication effects, metabolic derangements, and hypothermia. When using ancillary tests to confirm brain death, clinicians must consider the risks and limitations of these tests to avoid false-negative or false-positive diagnoses of brain death.

Confirmatory tests generally accepted by most centers include conventional cerebral angiography and EEG,[19] although nuclear medicine brain scintigraphy is being used increasingly more often in many centers in the United States. Consensus criteria are available for the use of EEG, somatosensory evoked potentials, and radionucleotide scan for the evaluation of brain death.[20,21] In 1999, the Therapeutics and Technology Assessment Subcommittee of the AAN accepted transcranial Doppler ultrasonography (TCD) as a reliable procedure for confirmation of brain death.[22] Following are descriptions of commonly used ancillary tests, categorized by the physiological measure of brain function they provide.

Measurements of Cerebral Blood Flow

Conventional Cerebral Angiography

A cerebral angiogram performed by injection of a contrast agent under high pressure into the aortic arch is consistent with brain death if the contrast agent

reaches both anterior and posterior circulations and there is absence of intracranial filling starting at the level of entry of the carotid and vertebral arteries into the skull. The external carotid circulation should be preserved, and delayed filling of the superior longitudinal sinus can be seen. Cerebral angiography is one of the most accepted modalities for confirmation of brain death, but it is the most invasive of all available ancillary tests.

Transcranial Doppler Ultrasonography

TCD insonation of bilateral cerebral arteries and anterior and posterior insonation windows should be performed. TCD signals consistent with brain death include (1) absent diastolic or reverberating flow that indicates flow only through systole or retrograde diastolic flow or (2) small systolic peaks in early systole that indicate very high vascular resistance. Of note, absence of TCD signals cannot be interpreted as confirmatory of brain death because 10% of all patients do not have temporal insonation windows. An exception to this rule may be considered in patients who have had known TCD signals that subsequently disappeared and who have other clinical history and examination findings consistent with the diagnosis of brain death.

If properly performed, TCD has 91.3% sensitivity and 100% specificity in determination of brain death.[23,24] However, accurate TCD study requires a trained and experienced operator, and between-operator and between-laboratory differences can occur. Reports have described finding TCD "brain death patterns" in patients who meet clinical brain death criteria but have persistent EEG activity. Small systolic peaks may also occur as transient phenomena in non-brain-dead patients with aneurysmal rupture. TCDs may be less reliable in patients with a prior craniotomy.

Isotope Angiography

Isotope angiography uses rapid intravenous injection of serum albumin labeled with technetium 99m followed by bedside imaging with a portable gamma camera. Absence of intracranial radioisotope activity in this study is consistent with the diagnosis of brain death. Filling of the sagittal and transverse sinuses may be seen in delayed images due to extracranial drainage of the circulation. The sensitivity and specificity of this technique have not been determined in adults, and this test is not commonly used for confirmation of brain death.

Technetium-99m-hexamethylpropyleneamineoxime (99mTc-HMPAO) Scan

This is a nuclear scintigraphy that measures brain perfusion and is now one of the most commonly used tests for confirmation of brain death. The 99mTC-HMPAO radioisotope should be injected intravenously within 30 minutes of reconstitution, and anterior and both lateral planar image counts (500,000) of the head should be obtained immediately after injection, between 30 and 60 minutes post injection, and then again at 2 hours post injection. Successful intravenous injection of radioisotope can be verified by obtaining additional images of the liver, although this is optional and not always performed. Absence of radionucleotide uptake in the entire brain parenchyma, or a "hollow skull sign," is consistent with the diagnosis of brain death.

Studies of Cerebral Activity and Reactivity

Electroencephalography

EEG should be performed with a minimum of 8 scalp electrodes with an interelectrode distance of at least 10 cm and an interelectrode impedance of 100 to 10,000 Ω. Sensitivity should be increased to at least 2μV, a high-frequency filter should be set at or above 30 Hz, and a low-frequency filter should be set at or below 1 Hz. At least 30 minutes of recording with appropriate calibrations should be performed. Once these specific technical requirements are met and in a patient whose clinical examination is consistent with loss of all brain function, EEG showing absence of electrical activity and lack of reactivity to intense somatosensory and audiovisual stimuli is consistent with the diagnosis of brain death. It is important to note that absence of electrical activity on EEG alone does not confirm brain death in the absence of clinical examination. Presence of any electrical activity on EEG rules out the diagnosis of brain death at the time the study is performed. Significant ICU-related artifacts may mimic electrical activity and complicate EEG interpretation.

Somatosensory Evoked Potentials

Standard somatosensory evoked potentials with bilateral median nerve stimulation and bilateral absence of N20-P22 responses are consistent with the diagnosis of brain death.

Other Tests

Other tests used to determine brain death include types of arterial imaging such as cerebral computed tomographic angiography and cerebral magnetic resonance imaging angiography; also used is xenon computed tomography, which evaluates

quantitative cerebral perfusion. There has been relatively little clinical experience with these techniques, and their sensitivities and specificities are not well known.

CRITICAL CARE SUPPORT DURING AND AFTER BRAIN HERNIATION AND DEATH BY NEUROLOGICAL CRITERIA

Patients who progress to meet death by brain criteria are often hemodynamically unstable during this process due to physiological and biochemical changes associated with their severe brain injury. Vasopressors alone are often insufficient in restoring hemodynamic stability and end-organ perfusion.[25] Hemodynamic instabilities often limit the ability of the care team to complete the process of determination of death by neurological criteria. Understanding the physiological and biochemical changes that occur during brain herniation as a patient progresses to brain death is important for successful support and stabilization of the patient during this critical time period.

Physiological Changes Associated With Severe Brain Injury and Brain Death

Sympathetic Surge and Cardiac Instability

Severe brain injury is often associated with a systemic sympathetic surge. This massive release of catecholamines is often associated with severe hypertension from increased systemic vascular resistance, neurogenic stunned myocardium or “voodoo heart” from cardiac contraction band necrosis, cardiac dysrhythmias, and neurogenic pulmonary edema. Neurogenic stunned myocardium may significantly reduce cardiac output and result in cardiogenic shock requiring inotropic support.

As patients progress through brain herniation toward brain death, some may develop severe hypertension, bradycardia, and irregular respirations, also known as “Cushing’s triad.” After patients are supported through this period and progress further toward brain death, their heart rates tend to stabilize and become monotonic as all central nervous system control of heart rate is lost.

Loss of Sympathetic Tone

Following the sympathetic surge and prior to brain death, the higher level sympathetic neurons are lost, and herniation of cerebellar tonsils results in higher

spinal cord infarction. These events result in generalized loss of sympathetic tone resulting in low systemic vascular resistance and this can lead to hypotension. Injury to the same anatomic area leads to loss of temperature control, and patients may become hypothermic while progressing toward brain death. Since brain death determination is not recommended when the core temperature is below 36°C (96.8°F), it is important to anticipate potential progressive hypothermia and maintain a core temperature above 36°C in this patient population.[12]

Pituitary Dysfunction

Pituitary hormone secretions become compromised and eventually cease as a patient progresses through brain herniation to brain death, and patients often manifest symptoms of pan-hypopituitarism during this process. Compression and infarction of the posterior pituitary in patients with impending brain death often result in significant central diabetes insipidus with free water diuresis leading to hypovolemia, hypernatremia, and ultimately hemodynamic collapse if left untreated. It is important to monitor for and timely treat central diabetes insipidus to prevent significant hypernatremia, hypovolemia, and possibly cardiovascular collapse in patient progressing through cerebral herniation. Monitoring for central diabetes insipidus includes regular assessment of urine output and urine specific gravity every 1-2 hours. If a patient develops increase in urine output with decreased urine specific gravity consistent with diabetes insipidus, vasopressin supplementation and free water replacement should be started to maintain serum sodium and intravascular volume in normal range.

In patients who eventually progress to brain death, serological studies show low systemic cortisol levels; hypothyroidism with low thyrotropin, triiodothyronine, and thyroxine; and low insulin levels. Supplementation of deficient hormones and appropriate volume resuscitation after onset of central diabetes insipidus may decrease vasopressor requirements and improve hemodynamic stabilization as a patient goes through the process of brain death determination.

Organ Donation Considerations

Potential organ donation falls into 3 general types: living organ donation, donation after cardiac death (DCD), and donation after neurological death (DND). DND donors are patients who meet criteria for brain death who are eligible for and whose families give consent for organ donation. They are also known as “beating heart donors.”

To date, most organ donations come from donation after neurological death (DND), and organ transplantation outcomes are superior following DND compared with DCD. Excellent critical care support to maintain hemodynamic stability and end-organ perfusion during and following the determination of death by brain criteria not only improves care of the patient but also significantly improves viability of organs, leading to more organs donated and better organ transplantation outcome.

Identification of Potential Donors

Within the United States, local organ donor networks can assist healthcare providers in the identification, screening, consent process, and management of potential organ donors. Local organ donor networks should be notified of all patients with impending brain death and patients with planned withdrawal of life-sustaining care.

Contraindications for organ donation include disseminated infection, history of certain cancers, certain viral infections (eg, rabies, active herpes simplex encephalitis, etc), and known prion diseases (such as Creutzfeldt-Jacob disease). Some apparent contraindications may only be relative. For example, patients with history of hepatitis C may donate to potential recipients who are also hepatitis C infected. Representatives from local organ donor networks can assist healthcare providers in identifying absolute versus relative contraindications to organ donation.

Consent Process

Local organ donor network teams take an active role in approaching families for consent in centers in the United States. Many healthcare providers find that maintaining a clear boundary between the patient care team and the organ donation team minimizes potential conflicts of interest and family confusion. Typically, the primary patient care team discusses the patient's clinical condition and goals of care with the family but does not participate in the discussion and consent process regarding organ donation. The primary patient care team alerts the local organ donor network of potential organ donation candidates, and representatives of the local organ donation network may then approach the family for discussion and consent for organ donation. However, different models are used in different centers, and in some centers the primary patient care team may participate in the discussion and consent process regarding organ donation.

Organ-Sparing Therapy

Organ-sparing therapy in a brain-dead donor includes maintenance of adequate systemic perfusion pressure and tissue perfusion and hormonal supplementation. Fluid resuscitation is often required to maintain euvolemia, and vasopressor supplementation is often required for hypotension secondary to low sympathetic tone. Hormone supplementation therapy generally includes supplementation with levothyroxine, methylprednisolone, insulin, and vasopressin. Successful delivery of organ-sparing therapy in a brain-dead donor improves organ donation rate and reduces the rate of subsequent graft dysfunction and graft loss.[25]

Table 3 summarizes hormone supplementation therapies in the management of a patient progressing to brain death, including potential indications and ranges of medication dose. Data on this topic are limited, and the optimal doses of hormone supplementation therapy in brain death are not known. Healthcare professionals should adjust the dosage of hormonal supplements in accordance with the donor's clinical condition.[26]

Table 3. Hormone Supplementation Therapies in Brain-Dead Organ Donors

Medication	Indication	Dosage
Thyroxine (T_4)	Impending brain death with hypotension and low systemic T_4	10-20 µg/h IV (IV bolus of T_4 can cause hyperglycemia. In patients with serum potassium >3.5 mEq/L, premedication with IV insulin and 50% dextrose is recommended.)
Vasopressin	Impending brain death with hypotension and diabetes insipidus (urine output >5 mL/kg/h for >2 h, urine specific gravity <1.005, serum sodium >45 mEq/L)	0.5-6 u/mL IV drip, titrate to urine output <5 mL/kg/h and systemic vascular resistance 800-1,200 (can also be given as IV push 1-4 µg every 6 h)
Insulin	Impending brain death with hyperglycemia	Insulin drip ≥1 µg/h; titrate to maintain normal serum glucose
Methylprednisolone	Impending brain death with hypotension	15 mg/kg/d IV bolus

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CHAPTER 5

Shock: Classification, Pathophysiological Characteristics, and Management

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Key word: shock

Shock was first described in 1737 by the French surgeon Le Dran,[1] who used the term in the setting of gunshot wounds to indicate a severe impact or jolt to the body. It was further refined in 1867 by Morris[2] to describe not only the trauma but the body's response to the insult. The definition has continued to evolve over the years with further advances in shock research, particularly with the military conflicts of the 1900s. Currently, shock is defined as inadequate tissue perfusion resulting in cellular injury. Ultimately, this causes the release of inflammatory mediators that further compromise tissue perfusion, resulting in organ failure and death unless quickly corrected.[3] Correction of the underlying process can reverse the progression of the shock state. Thus, the circulating volume must be identified and expanded quickly, and the underlying pathological process must be controlled.

In the shock state, effective tissue perfusion is decreased secondary to a global reduction in perfusion (ie, low cardiac output [CO] states), a maldistribution of the blood flow, or a defect in substrate utilization at the subcellular level.

Shock may well be the most common and important problem encountered in the ICU. Cardiogenic shock is one of the critical complications of ischemic heart disease and remains the number one cause of mortality in the United States. Hypovolemic shock and extracardiac obstructive shock are major contributors to trauma-associated morbidity and mortality. Finally, septic shock is the ninth leading cause of disease-related deaths in the United States.[4]

CLASSIFICATION OF SHOCK

Shock can be classified as hypovolemic, cardiogenic, extracardiac obstructive, distributive, and mixed (**Table 1**).

Table 1. Classification of Shock

Hypovolemic (Oligemic)
- Hemorrhagic
  - Trauma
  - Gastrointestinal
  - Retroperitoneal
- Fluid depletion (nonhemorrhagic)
  - External fluid loss
    - Dehydration
    - Vomiting
    - Diarrhea
    - Polyuria
- Interstitial fluid redistribution
  - Thermal injury
  - Trauma
  - Anaphylaxis
- Increased vascular capacitance (vasodilation)
  - Sepsis
  - Anaphylaxis
  - Toxins/drugs

Cardiogenic
- Myopathic
  - Myocardial infarction
    - Left ventricle
    - Right ventricle
  - Myocardial contusion (trauma)
  - Myocarditis
  - Cardiomyopathy
  - Postischemic myocardial stunning
  - Septic myocardial depression
  - Pharmacological
    - Anthracycline cardiotoxicity
    - Calcium channel blockers
- Mechanical
  - Valvular failure (stenotic or regurgitant)
  - Hypertrophic cardiomyopathy
  - Ventricular septal defect
- Arrhythmic
  - Bradycardia
    - Sinus (eg, vagal syncope)
    - Atrioventricular blocks
  - Tachycardia
    - Supraventricular
    - Ventricular

Extracardiac Obstructive
- Impaired diastolic filling (decreased ventricular preload)
  - Direct venous obstruction (vena cava)
    - Intrathoracic obstructive tumors
  - Increased intrathoracic pressure (decreased transmural pressure gradient)
    - Tension pneumothorax
    - Mechanical ventilation (with positive end-expiratory pressure or volume depletion)
- Decreased cardiac compliance
  - Constrictive pericarditis
  - Cardiac tamponade
    - Acute
    - Post–myocardial infarction free wall rupture
    - Traumatic
    - Hemorrhagic (anticoagulation)
  - Chronic
    - Malignant
    - Uremic
    - Idiopathic
- Impaired systolic contraction (increased ventricular afterload)
  - Right ventricle
    - Pulmonary embolus (massive)
    - Acute pulmonary hypertension
  - Left ventricle
    - Saddle embolus
    - Aortic dissection

Distributive
- Septic (bacterial, fungal, viral, rickettsial)
- Toxic shock syndrome
- Anaphylactic, anaphylactoid
- Neurogenic (spinal shock)
- Endocrinological
  - Adrenal crisis
- Thyroid storm
- Toxic (eg, nitroprusside, bretylium)

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Hypovolemic Shock

Hypovolemic shock results from a loss of blood or fluid. Decreased circulating blood volume leads to decreased diastolic filling pressure and volume, inadequate CO, hypotension, and shock.[5]

Cardiogenic Shock

Cardiogenic shock is marked by reduced cardiac function as a result of direct myocardial damage or mechanical abnormality, leading to a decrease in CO and blood pressure.

Extracardiac Obstructive Shock

Extracardiac obstructive shock results secondary to obstruction of flow in the cardiovascular circuit. This obstruction leads to inadequate diastolic filling or decreased systolic function secondary to an increase in afterload and a decrease in CO and blood pressure.

Distributive Shock

Distributive shock is characterized by vasodilatation, causing a decrease in preload that leads to hypotension with a normal or increased CO. Sepsis is an example of distributive shock. Myocardial depression frequently accompanies distributive shock. Typically, a decrease in systemic vascular resistance (SVR), an increase in CO, and a decrease in blood pressure are seen. These changes result from mediator effects at the microvascular level that produce inadequate blood pressure and cause multiorgan dysfunction.

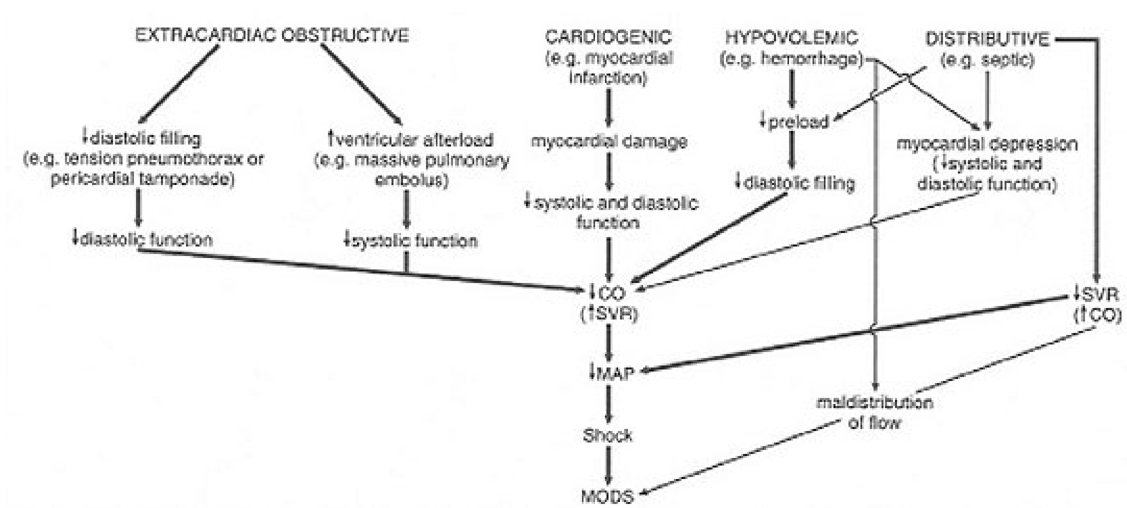
Mixed Shock

Mixed shock occurs when 2 or more processes occur simultaneously, such as when myocardial depression is seen in the face of septic shock.

PATHOPHYSIOLOGICAL CHARACTERISTICS OF SHOCK

Although the causes of shock differ, most involve similar biochemical and metabolic pathways. In essence, the cardiovascular system is unable to adapt to an insult, be it sepsis, blood loss, or trauma, such that CO and blood pressure are compromised (**Figure 1**). Blood pressure typically depends on the CO and SVR. The brain and heart are able to autoregulate blood flow over a wide range of blood pressures, from a mean arterial pressure (MAP) of 50 mm Hg up to 150 mm Hg, as seen in **Figure 2**.[6] Hence, a MAP below this range indicates a severe reduction in CO. Cardiac output is the product of heart rate (HR) and stroke volume (SV): CO = HR × SV. Stroke volume in turn depends on preload, afterload, and contractility. Preload is dependent on circulating volume, venous time, atrial contraction, and intrathoracic pressures and reflects end-diastolic ventricular volume. Clinically, we use central venous pressure (CVP) and pulmonary capillary wedge pressure as estimates of preload; however, these are not always reliable estimates. Afterload is the resistance to blood flow from the ventricle with each contraction. Left ventricular afterload is equated to the mechanical properties of the arterial side of the circulatory system. The SVR is our best tool to assess afterload clinically. *Contractility* refers to the intrinsic ability of the myocardial fibers to shorten under varying loads. Contractility is assessed via echocardiography, which is used to determine the ratio of peak systolic pressure to end-systolic volume. In the shock state, contractility is depressed because of acidosis, myocardial depressant factors, and ischemia, as seen in **Figure 3**.

Figure 1. The interrelationships between different forms of shock



The interrelationships between different forms of shock. For cardiogenic, hypovolemic, and obstructive shock, hypotension is primarily due to decreased cardiac output (CO) with systemic vascular resistance (SVR) rising secondarily. With distributive shock (and particularly septic

shock), hypotension is primarily due to a decrease in systemic vascular resistance with a secondary increase of cardiac output. In many forms of shock, the hemodynamic characteristics are influenced by elements of hypovolemia, myocardial depression (ischemic or otherwise), and vascular dysfunction (which may affect afterload). Dominant pathophysiological pathways are denoted by heavier lines.

Abbreviations: CO, cardiac output; MAP, mean arterial blood pressure; MODS, multiple organ dysfunction syndrome; SVR, systemic vascular resistance.

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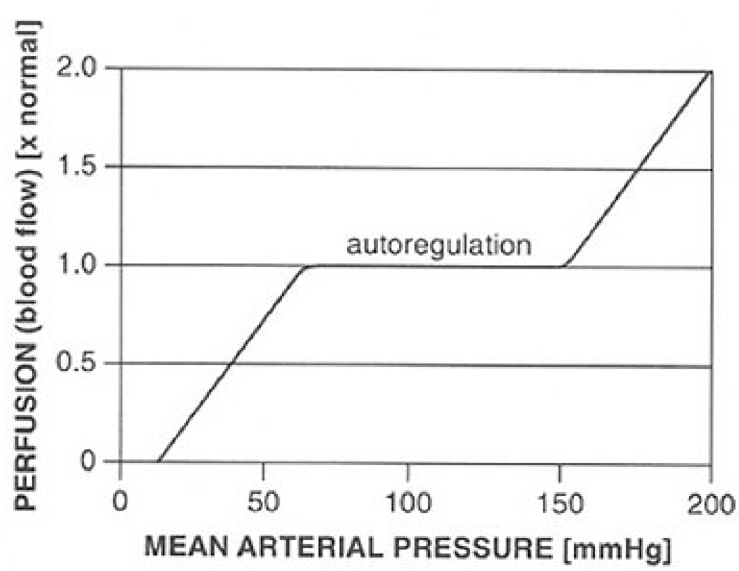
Figure 2. Idealized representation of blood flow autoregulation



Idealized representation of blood flow autoregulation. Within the autoregulatory range of blood pressure for a tissue or organ, perfusion can be held relatively constant. Outside this range, autoregulation fails and perfusion becomes a function of mean arterial pressure.

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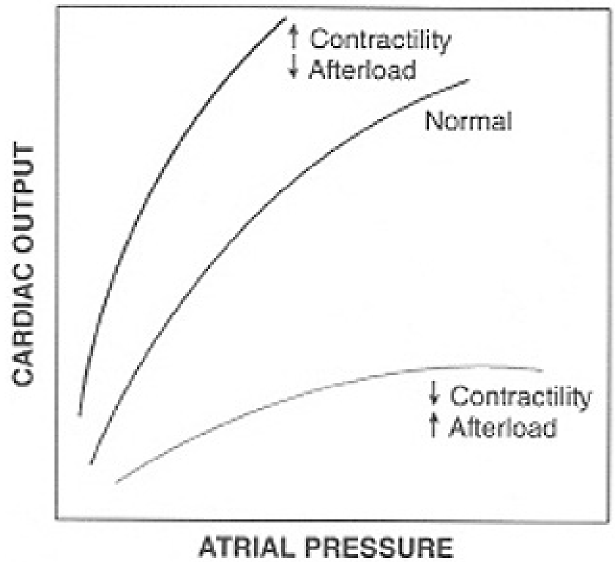
Figure 3. Cardiac function curve demonstrating the effect of variations of preload (atrial pressure), contractility, and afterload on cardiac performance.



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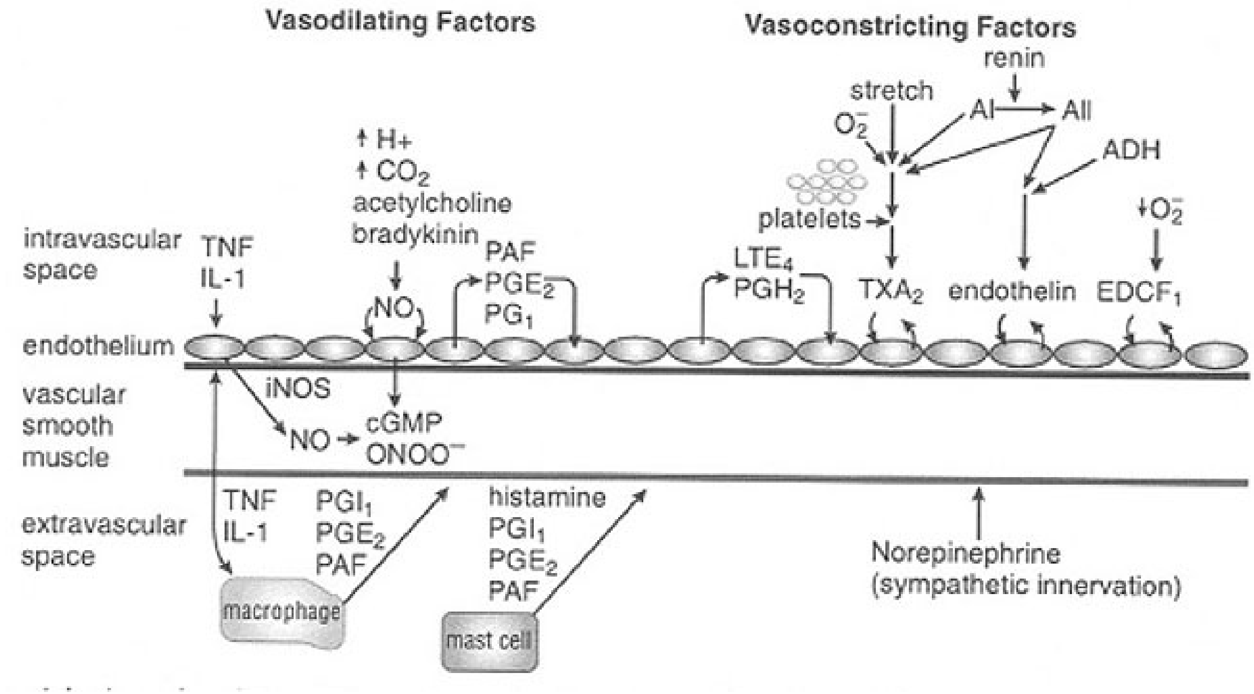
During shock, tissue perfusion is dictated by the microvascular system. CO distribution is complex and is determined by local intrinsic autoregulation and extrinsic regulation mediated by autonomic tone and hormonal factors. Blood flow to organs may be affected by microvascular regulation to maintain flow to those organs requiring the highest metabolic activity. Autoregulation of the blood flow occurs through 2 mechanisms. Changes in neurovascular tone are mediated through endothelial stretch receptors, such that as perfusion decreases, an opposing increase in vascular resistance occurs and overall perfusion is maintained. Additionally, the increased metabolic activity in the tissue causes an increase in carbon dioxide and hydrogen, resulting in vasodilatation and increased perfusion. Extrinsic control of vascular tone is exerted primarily through the autonomic nervous system (**Figure 4**). The release of acetylcholine leads to generation of nitric oxide and cyclic guanosine monophosphate generated in the endothelial cells and vascular smooth muscle, leading to vasodilatation. Increased sympathetic tone leads to norepinephrine release and the activation of more adrenoreceptors and increased vascular tone. Epinephrine and norepinephrine are released systemically from the adrenal medulla under stressful periods. Basal control of blood pressure is regulated by the renin-angiotensin system. Organ blood flow depends on the maintenance of blood pressure within defined ranges that vary from organ to organ. Good autoregulation exists between MAP of 60 and 100 mm Hg in the context of normal physiological status.[7] During periods of shock, the autoregulatory responses of most vascular beds are overwhelmed. The brain and heart have high

metabolic rates and a low storage of substrate and will not tolerate ischemia for long. Blood flow to these vital organs (heart and brain) is preserved because of dominant autoregulation of flow. Flow to other organs is decreased secondary to the decrease in CO as organ SVR increases to maintain blood pressure.[8] This adaptation preserves blood flow to vital organs with just a mild decrease in CO. If the insult continues, organ failure can develop. Even with resuscitation, microvasculature abnormalities can persist for days.[9] In the face of irreversible shock, the match of tissue demand and substrate supply worsens, leading to organ failure and death. The mechanisms include the following[5]:

- Tissue acidosis
- Catecholamine depletion and resistance to the effects of catecholamines
- Release of arachidonic acid and metabolites
- Decreased sympathetic tone
- Generation of nitric oxide by vascular smooth muscle (**Figures 4-6**)

Shock is also associated with disruptions of the endothelial cell barrier integrity, which normally maintains oncotic pressure within the circulatory space. With this loss, oncotic pressure falls, interstitial edema develops, and the circulating volume decreases. Microvascular clotting and microthrombi occur as well, leading to further endothelial cell injury (**Figures 4** and **5**).

Figure 4. Physiological and pathophysiological vasoactive factors



Physiological and pathophysiological vasoactive factors.

Abbreviations: AI, angiotensin I; AII, angiotensin II; ADH, antidiuretic hormone (vasopressin); cGMP, cyclic guanosine monophosphate; $EDCF_1$, endothelium derived contracting factor; IL-1, interleukin-1â; iNOS, inducible nitric oxide synthetase; LTE_4, leukotriene E_4; NO, nitric oxide; ONOO–, peroxynitrite; O_{2-}, superoxide anion; PAF, platelet activating factor; PGE_2, prostaglandin E_2; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; TNF, tumor necrosis factor-á; TXA_2, thromboxane A_2.

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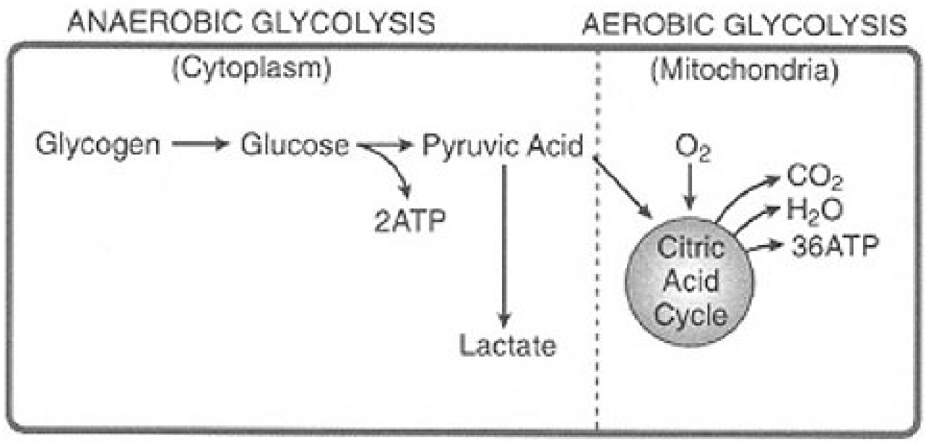
CELLULAR RESPONSE

As the interstitial transport of nutrients is impaired, intracellular adenosine triphosphate (ATP) stores decrease, likely caused by the uncoupling of oxidative phosphorylation. This decrease leads to the accumulation of hydrogen ions, lactate, and other by-products of aerobic metabolism. As shock progresses, these metabolites overrun vasomotor tone and result in further hypotension.[5]

Cellular dysfunction in shock is produced through 3 mechanisms: cellular ischemia, inflammatory mediators, and free radical injury, with cellular ischemia accounting for the majority of cell damage. This process is illustrated in **Figures 5** through **7**. Inadequate perfusion and hypoxia lead to anaerobic metabolism, which produces only 2 ATP molecules versus 36 during the breakdown of 1

molecule of glucose. This results in the depletion of ATP and intracellular acidosis, leading to a buildup of lactate. The energy-dependent ion transport pumps are unable to maintain the transmembrane potential, resulting in mitochondrial dysfunction, abnormal carbohydrate metabolism, and failure of energy-dependent enzyme reactions.

Figure 5. Mechanisms of cellular dysfunction and injury in shock



Mechanisms of cellular dysfunction and injury in shock. Cell injury is mediated by multiple mechanisms during shock. Tissue ischemia may result in limitation of aerobic ATP generation. This results in further mitochondrial impairment due to deficits of mitochondrial membrane function, altered signal transduction including decreased muscle contractility (ATP is the precursor of cyclic AMP), impaired energydependent maintenance of transmembrane potential and ion gradients, increased intracellular pH due to anaerobic metabolism, and possible initiation of autolytic mechanisms. Free radicals may result in broad injury to cellular membranes, resulting in impaired maintenance of transmembrane potential and ion gradients, mitochondrial generation of ATP, and activation of autolytic pathways involving DNA degradation and lysosomal rupture (apoptosis). Various circulating mediators (including cytokines, kinins, eicosanoids, and complement components) may result in mitochondrial dysfunction, signal transduction abnormalities, membrane protein channel alterations, and possibly alterations of gene expression. Any of these may lead to cell death through metabolic failure and lysosomal enzyme release.

Abbreviations: b-AR, b-adrenergic receptor; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; GP, G proteins; NO, nitric oxide; NOS, nitric oxide synthetase.

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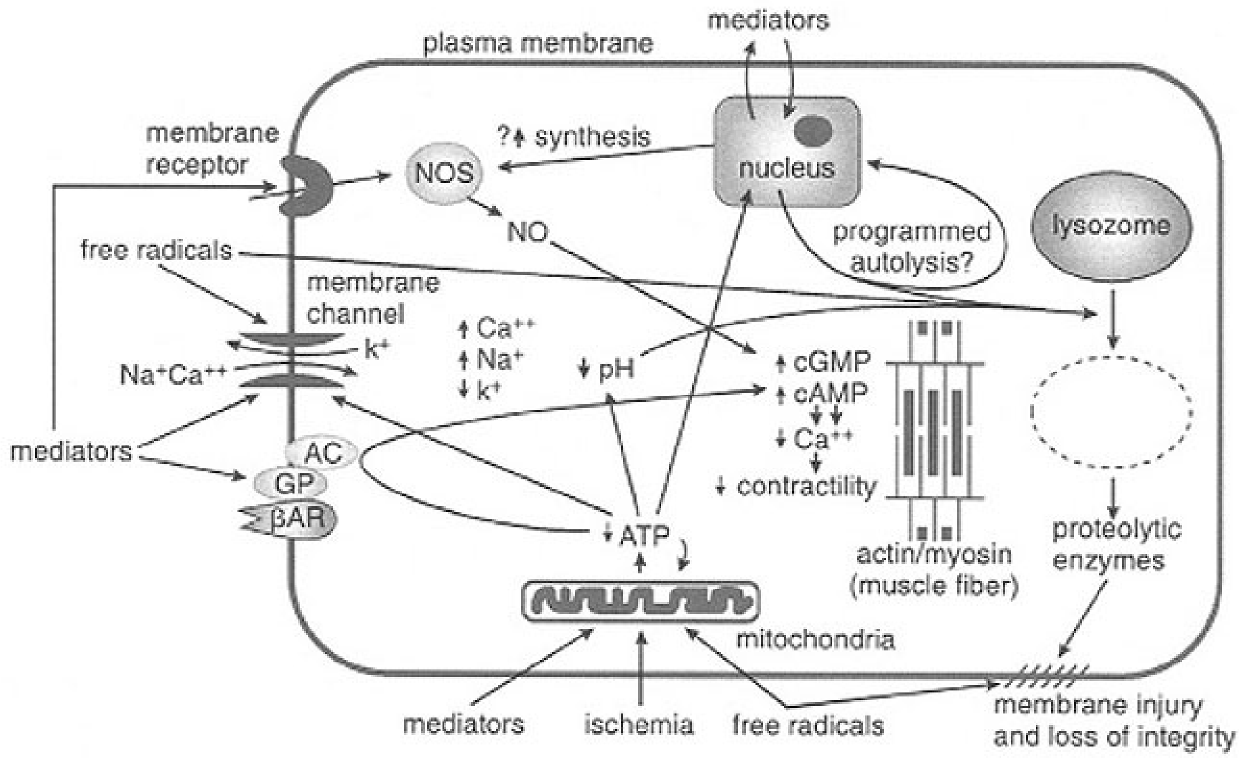
Figure 6. Aerobic and anaerobic glucose metabolism



Aerobic and anaerobic glucose metabolism. Under anaerobic conditions, pyruvic acid cannot enter the citric acid cycle in the mitochondria (in order to optimally produce adenosine triphosphate [ATP]) and is shunted to lactate in the cytoplasm. This produces fewer high-energy phosphates per mole of glucose metabolized. Hydrolysis of ATP molecules in an anaerobic environment results in production of hydrogen ions that cannot be metabolized or cleared resulting in intracellular acidosis.

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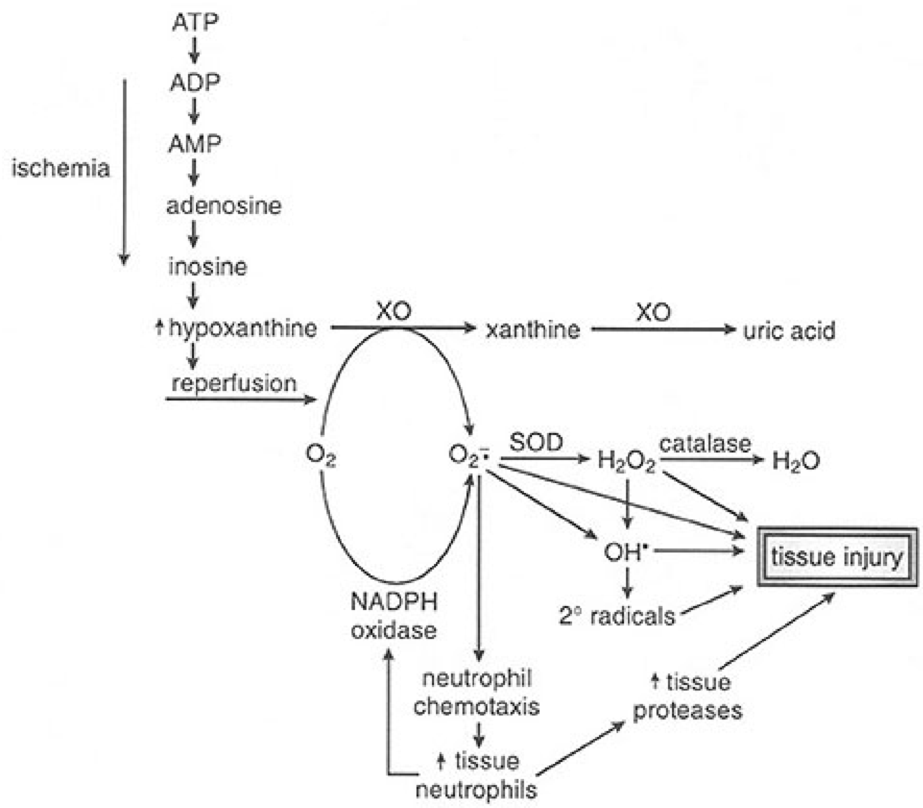
Figure 7. Free radical-mediated tissue injury



Free radical-mediated tissue injury. Superoxide (O_{2-}) is primarily produced in shock from hypoxanthine (a metabolite of adenosine triphosphate [ATP] degradation) by xanthine oxidase (XO) during reperfusion post ischemia. Superoxide can be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and then to H_2O or may be converted to the highly reactive hydroxyl (OH·), which mediates tissue injury. Free radical tissue injury may be amplified by superoxide recruitment of neutrophils, which secondarily produce additional superoxide through NADPH oxidase.

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Cellular ischemia occurs as a result of the supply dependence on oxygen and the imbalance between the supply of oxygen and the demand of the tissues. The critical value seems to be 8 to 10 ml O_2/100 gm/min. In the patient with sepsis, acute respiratory distress syndrome, or trauma, there is a pathological oxygen supply dependency.

Inflammatory mediators lead to inadequate perfusion or cause direct cell injury to the cells in a number of organs. Tumor necrosis factor and interleukin 1 may directly injure cells by causing transmembrane ion gradient dysfunction. Tumor necrosis factor stimulates the release of other mediators including cytokines, platelet activating factor, leukotrienes, prostaglandins, and thromboxane.

Typically, the release of the inflammatory mediators benefits the host by increasing blood flow to damaged tissues and activating host defenses. In sepsis, the response becomes excessive and is unregulated. Free radicals occur after ischemia and reperfusion, which can inactivate proteins, damage DNA, induce lipid peroxidation, and lead to cell death and tissue injury (**Figures 4** and **7**). Apoptosis can occur as heat shock proteins interfere with synthetic pathways and initiate programmed cell death. This process is illustrated in **Figure 6**. Genetic studies have shown an association between the presence of the tumor necrosis factor allele 2 and a high risk for septic shock and death.

As described above, the proinflammatory response attacks the invading pathogens perhaps at the expense of tissue damage, the anti-inflammatory response limits inflammation and thus makes the host more vulnerable. Sepsis is considered an imbalance between the pro- and anti-inflammatory responses of the body.

Compensatory mechanisms in shock attempt to maintain effective tissue perfusion by stimulating the sympathetic nervous system; releasing hormones such as angiotensin II, norepinephrine, epinephrine, and vasopressin; and enhancing the unloading of oxygen. This compensation is briefly effective but then becomes overwhelmed by the ongoing shock and subsequent tissue damage.

MANIFESTATIONS OF SHOCK

During periods of shock, multiple organs are affected by varying degrees. This diffuse damage leads to multiple organ failure.

Central Nervous System

Cerebral perfusion is impaired in shock, but flow remains relatively well preserved until MAP is less than 50 mm Hg.[10] Ischemic injury eventually will be seen in the area most sensitive to ischemia—the cerebral cortex. As cerebral perfusion falls the patient may have an altered level of consciousness ranging from confusion to coma.

Heart

Sympathoadrenal stimulation causes an increase in HR that can lead to supraventricular tachycardia or ventricular ectopy in the setting of ischemia. Just

like the blood supply to the brain, the blood supply to the heart is autoregulated, making it relatively resistant to the sympathetically driven vasoconstriction and hypoperfusion injury seen in shock. Contractility is increased in most forms of shock, especially early in the process. Hypotension is associated with decreased coronary artery perfusion pressure, which may lead to ischemia in patients with coronary artery disease. Circulating myocardial depressant factor is seen in septic, hemorrhagic, and cardiogenic shock.[11,12]

Respiratory System

Patients often experience an increase in minute ventilation with resultant hypocapnia and respiratory alkalosis. Ultimately, an increased work of breathing and impairments of respiratory and muscle function (from hypoperfusion) may lead to respiratory failure. A secondary risk is acute respiratory distress syndrome caused by fibrin neutrophil aggregates in the pulmonary microvasculature, inflammatory damage to the interstitium and alveoli, and exudation of proteinaceous fluid into the alveolar space.

Kidney

Acute renal failure increases mortality 35% to 80% in the setting of shock.[13] The kidney is moderately autoregulated, maintaining glomerular perfusion by increasing efferent arteriolar tone. Cortical and medullary ischemic injury occurs late in shock, resulting in acute tubular necrosis. Clinically, this presents with an initial decrease in urine output followed by an increase in serum urea nitrogen and creatinine over the next several days. Differentiating the cause of a decrease in urine output between a renal and a prerenal condition may be difficult (**Table 2**).

Table 2. Differentiation of Prerenal and Renal Causes

		UNa	**Fe Na**	**Uosmo**
Prerenal	Benign urine sediment	<20 mEq/L	<1%	<450 mOsm/L
ATN	Hematuria granular casts	>40 mEq/mL	2%	<350 mOsm/L
In cirrhosis and CHF		<20 mEq/L	<1%	

Abbreviations: ATN, acute tubular necrosis; CHF, congestive heart failure; Fe, iron; Na, sodium;

U_{Na}, urine sodium; Uosmo, urine osmolality.

Gastrointestinal Tract

The splanchnic circulation is very sensitive to sympathetic vasoconstriction. Ileus, gastritis, pancreatitis, acalculous cholecystitis, and colonic submucosal hemorrhage can be seen. Ischemia of the gut can lead to translocation of bacteria from the gut to the circulation.[14]

Similarly, the liver may exhibit elevated transaminases and lactate dehydrogenase. The values typically peak in 1 to 3 days and then normalize as the shock state is reversed.

Hematological System

Shock can cause disseminated intravascular coagulation (DIC) by activation of the coagulation and fibrinolysis cascades. The clinician can differentiate sepsis and DIC by measuring the level of factor VIII, which is normal or increased in hepatic dysfunction. Unless a patient has extensive trauma or bleeding, DIC is not seen with hemorrhagic shock. Thrombocytopenia, which is dilutional, is commonly seen following resuscitation.[15]

Metabolic System

Hyperglycemia is commonly seen in shock secondary to a decrease in insulin release. Additionally, epinephrine release results in skeletal muscle insulin resistance in order to preserve glucose for the heart and brain. Another common metabolic derangement is increased protein catabolism, resulting in a negative nitrogen balance.

Immune System

Immune dysfunction likely contributes to late mortality in septic shock. The mucosal barrier of the gut may be disrupted, leading to translocation of bacteria. Inflammation, ischemia, and free radical injury occur, as well as dysfunction of the cellular and humoral immune system. Medications used in resuscitation also can play a role. Dopamine suppresses the pituitary production of prolactin, which suppresses the T-cell proliferative response.[16] This immunological dysfunction may account for the ultimate mortality of patients late in their course from ongoing sources of infection.

THERAPEUTICS

Shock is a life-threatening emergency that must be recognized immediately and treated aggressively. Although early identification of the cause of the shock is important, studies often cannot be done immediately given the patient's severity of illness and inability to be moved. Patients typically present with hypotension, tachycardia, tachypnea, and oliguria. The extremities are cool and may become mottled. The patient may have an altered mental status. Clues may be available to differentiate among the causes of shock, such as the following examples:

- Patients with cardiogenic shock often have jugular venous distension, an S_3 and S_4, and regurgitation murmurs.
- With pulmonary embolus, patients present with hypoxia, dyspnea, and elevated pressures in the right side of the heart.
- In cardiac tamponade, the patient often has pulsus paradoxus and distant heart tones.
- Patients with septic shock may have fevers and chills and usually have a nidus of infection.

Laboratory Studies

Common findings include the following:

- Low or high white blood cell count with a left shift and bands
- High or normal hemoglobin levels (unless hemorrhagic shock is present)
- High to low platelet counts
- Low serum bicarbonate levels
- High anion gap
- High or normal creatinine levels
- High lactate levels

Hemodynamic Monitoring

Hemodynamic monitoring should be initiated if the patient does not respond to

initial therapy. If the patient requires vasopressors, arterial pressure monitoring is useful. Likewise, SVP monitoring may be useful to guide volume resuscitation, given that CVP may not reflect the actual intravascular volume in all patients. **Table 3** depicts hemodynamic parameters seen in the various forms of shock. Controversy surrounds the use of pulmonary artery catheters in shock, and most studies have documented no benefit in mortality.[17-19] Some information can be gleaned by waveform analysis such as looking for a step-up in oxygenation and following the patient's response to therapeutic interventions. The level of mixed venous oxygen saturation (SvO_2), obtained via either CVP or a pulmonary artery catheter, is a useful parameter to follow during resuscitation. As perfusion increases, SvO_2 rises, and vice versa. A normal SvO_2 is 65% to 75%. Lactate levels begin to increase when the SvO_2 falls below 30%.

Table 3. Hemodynamic Profiles of Shock[a]

Diagnosis	**CO**	**SVR**	**PWP**	**CVP**	**Svo_2**
Cardiogenic shock Caused by myocardial dysfunction [A]	↓↓	↑	↑↑	↑↑	↓
Caused by a mechanical defect Acute ventricular septal defect [B]	LVCO ↓↓ RVCO > LVCO	↑	nl or ↑	↑↑	↑ or ↑↑
Acute mitral regurgitation [C]	Forward CO ↓↓	↑	↑↑	↑ or ↑↑	↓
Right ventricular infarction [D]	↓↓	↑	nl or ↑	↑↑	↓
Extracardiac obstructive shock Pericardial tamponade [E]	↓ or ↓↓	↑	↑↑	↑↑	↓
Massive pulmonary emboli [F]	↓↓	↑	nl or ↓	↑↑	↓
Hypovolemic shock [G]	↓↓	↑	↓↓	↓↓	↓
Distributive shock Septic shock [H]	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑
Anaphylaxis	↑↑ or nl, rarely ↓	↓ or ↓↓	↓ or nl	↓ or nl	↑ or ↑↑

Comments

A: Usually occurs with evidence of myocardial infarction (>40% of left ventricular myocardium nonfunctional), severe cardiomyopathy, or myocarditis

B: If shunt is left-to-right, pulmonary blood flow is greater than systemic blood flow; oxygen saturation “step-up” (≥5%) occurs at right ventricular level; ↑ SvO_2 is caused by left to right shunt

C: Large V waves (≥10 mm Hg) in pulmonary wedge pressure tracing

D: Elevated right atrial and right ventricular filling pressures with low or normal pulmonary wedge pressures

E: Dip and plateau in right and left ventricular pressure tracings. The right atrial mean, right ventricular end-diastolic, pulmonary artery end-diastolic, and pulmonary wedge pressures are within 5 mm Hg of each other

F: Usual finding is elevated right-sided heart pressures with low or normal pulmonary wedge pressure

G: Filling pressures may appear normal if hypovolemia occurs in the setting of baseline myocardial compromise

H: The hyperdynamic circulatory state (↑ CO, ↓ SVR) associated with distributive forms of shock usually depends on resuscitation with fluids; before such resuscitation, a hypodynamic circulation is typical

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Abbreviations: CO, cardiac output; CVP, central venous pressure; LV, left ventricular; nl, normal; PWP, pulmonary wedge pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; ↑↑ or ↓, mild to moderate increase or decrease; ↑↑ or ↓↓, moderate to severe increase or decrease.

[a]The hemodynamic profiles summarized in this table refer to patients with the diagnosis listed in the left column who are also in shock (mean arterial blood pressure <60-65 mm Hg).

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Appropriate resuscitation from shock requires achievement of an adequate CO and MAP. Recent studies support the concept that the speed of implementation may be related to improved outcomes. This is seen in the golden hour in hypovolemic shock with trauma, the early use of antibiotics with septic shock,[20] and early reperfusion in cardiogenic shock secondary to myocardial infarction.

Resuscitation involves first assessing respiratory status and securing the airway. Oxygenation and ventilation must be ensured with a goal of oxygen saturation 90% or greater. Full ventilator support must be given to decrease the systemic oxygen demand being used by the respiratory muscles. Up to 30% of oxygen consumption can be consumed by the respiratory muscles in the shock state.

Circulatory shock is treated with aggressive volume resuscitation with crystalloids. Patients with cardiomyopathy may require higher filling pressures,

whereas patients with ARDS and altered vascular permeability may fare better with lower pressures. The use of colloid versus crystalloid for resuscitation is controversial. In a large randomized study of albumin versus normal saline, resuscitating with albumin did not show a benefit in outcome.[21] Subgroup analysis suggests some benefit in resuscitating patients with albumin in the setting of severe sepsis or for patients with very low serum albumin levels.[22] Hetastarch is a volume expander, but its use is limited in patients with renal failure and those who might experience dilutional coagulopathy.[23] Blood product transfusion is a controversial topic. One study showed that a hemoglobin level of 7 g/dL is appropriate for most patients, but anytime a transfusion is considered, the risks and benefits of giving blood products must be considered.[24,25]

Once the intravascular volume is optimized, the next line of therapy includes vasopressors and inotropes. **Table 4** summarizes the various vasopressors. Typically, the initial vasopressor used for circulatory shock is norepinephrine, a potent vasoconstrictor and inotrope. Norepinephrine appears to provide a more reliable increase in blood pressure than does dopamine. However, dopamine can be considered as well. At lower doses, dopamine has a mild inotropic effect as well as some renal effects. At higher doses, dopamine causes vasoconstriction. Dopamine can cause tachycardia and arrhythmias and has a higher incidence of mesenteric ischemia than norepinephrine.[26,27] Epinephrine is the first line of therapy in anaphylactic shock and is useful to support the patient post cardiopulmonary bypass. Epinephrine has both inotropic and vasopressor effects, and it is associated with mesenteric ischemia. Phenylephrine is a pure a-agonist and is used intraoperatively and in patients who have an underlying tachycardia. Vasopressin has been used in septic shock when other vasopressors have failed to normalize blood pressure. Vasopressin decreases CO and HR while increasing blood pressure and pulmonary artery pressure. Vasopressin may increase myocardial ischemia via a decrease in coronary blood flow, which may lead to myocardial infarction.

Inotropes such as dobutamine are useful. Dobutamine stimulates both the β_1 and β_2 receptors, thus increasing CO while decreasing SVR. Milrinone is a phosphodiesterase inhibitor that induces a positive inotropic state. It is a potent vasodilator that decreases both pulmonary vascular resistance and SVR. When choosing the initial pharmacological support for a given patient, the clinician must consider the physiological abnormalities that are present in that patient's shock state.

Table 4. Relative Potency of Intravenously Administered Vasopressors/Inotropes Used in Shock[a]

	Dose	Cardiac	
		Heart Rate	Contractility
Dopamine	1–4 μg/kg/min	1+	1–2+
	5–10 μg/kg/min	2+	2+
	11–20 μg/kg/min	2+	2+
Norepinephrine	2–20 μg/min	2+	2+
Dobutamine	1–20 μg/kg/min	1–2+	3+
Dopexamine[b]	0.5–6 μg/kg/min	2+	1+
Epinephrine	1–8 μg/min	4+	4+
Phenylephrine	20–200 μg/min	0	1+
Isoproterenol	1–8 μg/min	4+	4+
Vasopressin	0.04–0.12 μ/min (start 0.02–0.04 μ/min; filtrate up 0.02–0.04 μ/min every 20–30 min)	0	0
Milrinone	37.5–75 μg/kg bolus over 10 min; 0.375–0.75 μg/kg/min infusion	1+	3+

Abbreviation: CHF, congestive heart failure.
[a]The 1-4+ scoring system represents an arbitrary quantitation of the comparative potency of different vasopressors/inotropes.
[b]Not clinically released in the United States.

Table 4 continued

	Peripheral Vasculature			Typical Clinical Use
	Vasoconstriction	Vasodilitation	Dopaminergic	
Dopamine	0	1+	4+	All shock
	1–2+	1+	4+	
	2–3+	1+	4+	
Norepinephrine	4+	0	0	Refractory shock
Dobutamine	1+	2+	0	CHF; cardiogenic,

				obstructive and septic shock
Dopexamine[b]	0	3–4+	4+	CHF; cardiogenic shock
Epinephrine	4+	3+	0	Refractory shock or anaphylactic shock
Phenylephrine	4+	0	0	Neurogenic or septic shock
Isoproterenol	0	4+	0	Cardiogenic shock (bradyarrhythmia), torsade de pointes, ventricular tachycardia
Vasopressin	4+	0	0	Vasodilatory (e.g. septic) shock
Milrinone	0	2+	0	CHF; cardiogenic shock

Abbreviation: CHF, congestive heart failure.
[a]The 1-4+ scoring system represents an arbitrary quantitation of the comparative potency of different vasopressors/inotropes.
[b]Not clinically released in the United States.

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CLINICAL APPROACH TO SHOCK

The immediate goals in shock are to restore blood pressure and circulating volume. Goals are to achieve a MAP greater than 60 mm Hg, CVP greater than 8 mm Hg, and cardiac index greater than 2.2 L/min/m^2 in an effort to maintain oxygen delivery and prevent organ dysfunction.

Hypovolemic shock is characterized by a decrease in preload, which in turn decreases filling pressures and blood pressure. Hypovolemic shock can be caused by dehydration, hemorrhage, gastrointestinal fluid losses, urinary losses, or increased vascular permeability from sepsis. Patients have tachycardia, hypotension, decreased filling pressures, low urine output, altered mental status, and cool, clammy, mottled skin. The severity of hypovolemic shock depends on both the amount and the severity of fluid loss. Acute loss of 10% of circulating blood volume results in tachycardia and an increase in SVR, but blood pressure is maintained. A loss of 20% to 25% results in mild hypotension. At this point,

cardiac output starts to decrease and lactate production begins. With a loss of 40% of circulating blood volume, the patient becomes hypotensive and displays signs of shock indicating tissue hypoperfusion, activation of the inflammatory cascade, and widespread cellular damage. Rapid reversal of this process with blood, colloid, or crystalloid is required.

Cardiogenic shock results from failure of the heart as a pump. Cardiogenic shock can be caused by myocardial, valvular, or structural abnormalities. It is the most common cause of in-hospital mortality in patients with Q-wave myocardial infarctions. The patient has increased ventricular preload with increases in pulmonary capillary wedge pressure and CVP as well as ventricular volume. This process results in a decrease in cardiac index, SV, and MAP as a result of the failing pump. Patients have signs of congestive heart failure, an S_3, elevated neck veins, and peripheral hypoperfusion. Mortality is lower for cardiogenic shock caused by surgically correctable lesions. In the setting of left ventricular infarct, management options include intra-aortic balloon pump, cardiac angiography, and revascularization, as well as more novel mechanical devices such as ventricular assist devices (eg, with right-sided infarcts, fluids and inotropes are the mainstay of therapy, and pulmonary artery catheter monitoring may be helpful to guide therapy. Valvular or mechanical abnormalities may warrant echocardiogram, cardiac catheterization, and surgery.

Extracardiac obstructive shock results from obstruction to flow in the cardiovascular circuit. Causes include cardiac tamponade, constrictive pericarditis, and pulmonary embolus. Cardiac tamponade and constrictive pericarditis impair diastolic filling of the right ventricle. Hemodynamically, increased and equalized right and left ventricular diastolic pressures usually develop. Acute pulmonary embolus results in failure of the right side of the heart and entails elevated pulmonary artery and right-side heart pressures with low or normal left-side filling pressures. Other causes of obstructive shock include tension pneumothorax and mediastinal tumors. As with other types of shock, the acuity of the shock affects the body's ability to compensate. An acute accumulation of as little as 150 mL of blood in the pericardium can result in immediate tamponade and shock (eg, bleeding after cardiac surgery); conversely, the slow accumulation of 1 to 2 L of fluid can occur before the patient shows signs of shock (eg, tuberculous or uremic pericarditis). Management requires a quick diagnosis, which often can be made with echocardiogram. If cardiac tamponade is diagnosed, pericardiocentesis or surgical drainage is needed. In the case of a pulmonary embolus diagnosis (usually made by chest computed

tomography), heparin is initiated, and in the case of profound shock and hypoxia, thrombolytic therapy or an embolectomy should be considered.

Distributive shock is defined by a loss of peripheral resistance, septic shock being the leading example. Other examples include anaphylaxis, drug overdose, neurogenic causes, and Addisonian crisis. Sepsis involves early activation of both proinflammatory and anti-inflammatory responses. The process entails an overall decrease in SVR and fluid leak from the microvasculature, leading to inadequate intravascular volume and decreased preload. Volume resuscitation improves the preload. Characteristically, a normal or elevated CO, normal SV, and tachycardia are seen as well as hypotension. Myocardial depression is seen also, which is characterized by decreased stroke work in response to volume loading, biventricular reduction in ejection fraction, and ventricular dilatation. Tachycardia is an attempt to compensate for the depressed ejection fraction and to maintain SV. Treatment involves identification of the source of infection and drainage or removal of a foreign body, if possible. Appropriate antibiotic therapy, fluid resuscitation, and vasopressors or inotropes should be initiated as needed to optimize blood pressure and CO. Most patients with severe sepsis will require ventilator support for respiratory failure. This should be initiated early in the patient's course to improve work of breathing.

Sepsis and septic shock have been redefined by the Third International Consensus Conference Sepsis Definitions Task Force, which provides a more usable framework based on current evidence and clinical criteria. This is discussed further in **Chapter 9**.

Anaphylactic shock is a type of distributive shock caused by release of mediators from mast cells and basophils. It is an immediate hypersensitivity reaction mediated by the interaction of the antibodies on the surface of the mast cell and basophil with the appropriate antigen. Anaphylactic shock can be triggered by insect envenomations, drugs (particularly antibiotics), and, less frequently, heterologous serum, blood transfusions, immunoglobulin, and egg-based vaccines. Anaphylactoid reactions result from direct nonimmunological release of mediators from mast cells and basophils and also can lead to shock. These reactions can be caused by ionic contrast media, opiates, protamine, dextran and hydroxyethyl starch, muscle relaxants, and anesthetics. Hemodynamic features of anaphylactic shock are similar to those of septic shock. In addition to these findings, urticaria, angioedema, laryngeal edema, and severe bronchospasm can occur. Treatment consists of stopping or removing the offending agent and administering steroids, diphenhydramine, histamine (H_1 and H_2) blockers, and

epinephrine for hemodynamic instability.

Neurogenic shock involves loss of peripheral vasomotor control secondary to injury or dysfunction of the nervous system. Examples include shock associated with spinal injury, vasovagal syncope, and spinal anesthesia. These conditions are usually self-limited and transient, depending on the inciting cause. Therapy includes volume repletion and vasopressor support.

Adrenal crisis is uncommon and difficult to differentiate from other types of shock. It is life-threatening and requires prompt diagnosis and management. In the critical care setting, adrenal crisis can arise from bilateral adrenal hemorrhage in conjunction with overwhelming infections like meningococcal infections or HIV. Adrenal crisis also can be seen with anticoagulation, fungal infections, and malignancy. In the ICU it is not uncommon to see an inadequate adrenal response leading to hypotension. Adrenal crisis is treated with steroids and fluid resuscitation as needed.

SUMMARY

- Shock: Clinical syndrome resulting from a reduction in tissue perfusion that leads to cellular injury from the inadequate delivery of oxygen and substrate to the tissue. This process causes the release of inflammatory mediators that further compromise perfusion of the tissues.
- Hypovolemic shock: Shock resulting from a loss of blood or fluid. Decreased circulating blood volume leads to decreased diastolic filling pressure and volume, inadequate CO, hypotension, and shock.
- Cardiogenic shock: Reduced cardiac function resulting from direct myocardial damage or mechanical abnormality that leads to a decrease in CO and blood pressure.
- Extracardiac obstructive shock: Obstruction to flow in the cardiovascular circuit that leads to inadequate diastolic filling or decreased systolic function secondary to an increase in afterload and decreases in CO and blood pressure.
- Distributive shock: Shock characterized by vasodilatation that leads to a decrease in preload, which causes hypotension with a normal or increased CO.

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CHAPTER 6

Hemodynamic Monitoring

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Key words: hemodynamic monitoring, cardiovascular function, minimally invasive monitoring, pulmonary artery catheter, shock, thermodilution

The purposes of hemodynamic monitoring are to characterize the cardiovascular state of the individual, identify cardiovascular insufficiency and its most probable causes, and monitor response to targeted therapies aimed at restoring cardiovascular sufficiency. The previous chapters outlined the various forms of circulatory shock. Within this physiological framework, the interpretation of data derived from hemodynamic monitoring arises. Circulatory shock and systemic hypotension are medical emergencies, because if sustained, even for a short time, they will result in end-organ dysfunction and increased morbidity and mortality. Once arterial pressure and organ perfusion pressure are restored, resuscitation efforts focus on providing adequate oxygen (O_2) delivery (DO_2) to meet metabolic demand and reverse any existing tissue hypoperfusion. The choice of monitoring techniques must be individualized. In general, if accurate, noninvasive continuous monitoring is available, it is preferred to invasive intermittent monitoring. In reality, some degree of invasiveness is often required to continuously and accurately assess physiological data in the critically ill patient.

The principal biomarkers for hemodynamic monitoring discussed in this chapter are arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, and cardiac output (CO); the chapter also discusses the various ways of assessing oxygenation and tissue blood flow and their associated derived parameters. All vascular monitoring that uses fluid-filled catheters connected to electronic pressure transducers requires the following elements in order to measure dynamic and mean pressure and to enable arterial

pressure–derived estimates of CO: an open tubing system that is unobstructed at the tip (obstruction often occurs due to blood clots), noncompressible fluid, a mechanism to eliminate air bubbles in the tubing that dampen the signal, and hydrostatic zeroing to the phlebostatic point (5 cm below the manubrium sterni). Similarly, measures of CO by indicator dilution require complete indicator mixing, no early recirculation (eg, intracardiac shunts), and an appropriate sensor. All commercially available indicator dilution devices have sufficiently accurate sensors, so most measurement errors come from incomplete indicator mixing or early recirculation artifacts.

ARTERIAL BLOOD PRESSURE

Arterial blood pressure is the primary force driving blood into the tissues. Thus, hypotension is a medical emergency because it not only causes tissue hypoperfusion but also effectively abolishes normal autoregulation of blood flow distribution. Furthermore, owing to baroreceptor feedback and the increased use of b-adrenergic blocking agents, often neither tachycardia nor hypotension occurs in shock until the final terminal stages. With the exception of patients with sepsis, hypotension occurs only after normal sympathetic reflex mechanisms have been exhausted. Thus, waiting for hypotension to occur prior to resuscitation is to wait too long.

Blood pressure varies phasically with each heartbeat. Systolic pressure is the maximum pressure during ventricular ejection, and diastolic pressure is the lowest pressure in the blood vessels between heartbeats during ventricular filling as the stored arterial blood runs off into the periphery. The systolic to diastolic pressure difference is called the *pulse pressure* and is determined by left ventricular (LV) stroke volume, central arterial capacitance, and, to a certain extent, the rate of LV ejection. Since the arterial circuit is elastic and functions as both a capacitor for the ejected blood and an outflow resistor to prevent rapid decreases in arterial pressure in diastole, both systolic and diastolic pressures vary across the vascular tree. Systolic pressure usually increases from central to peripheral sites, whereas diastolic pressure decreases slightly. Mean arterial pressure (MAP), estimated as the sum of diastolic pressure plus one-third of the pulse pressure, is the primary input driving pressure for cerebral and peripheral organ perfusion. Coronary perfusion is primarily determined by diastolic arterial pressure because cardiac contraction during systole otherwise stops intramyocardial blood flow. Importantly, MAP is constant throughout the large to medium-sized arteries because these central arteries have almost no

measurable resistance. Finally, a low diastolic pressure reflects vasodilation because even in severe low-output states, diastolic arterial pressure is usually maintained as pulse pressure decreases.

Noninvasive Measures of Arterial Pressure

The most common way of measuring arterial pressure is with a sphygmomanometer. This is often automated using an oscillatory algorithm that senses flow. A fundamental distinction is noted between the numerous automatic blood pressure measures currently used in hospitals and auscultation-defined measures of blood pressure using Korotkoff sounds. In an unstable patient, the noninvasive automatic measures of blood pressure oscillatory sensing algorithm degrades making its use for titration of vasoactive care undesirable. In these patients, blood pressure should be measured manually with a stethoscope. Sphygmomanometric measurements of blood pressure often give slightly higher systolic pressure and lower diastolic pressure than those reported from simultaneous direct measurement using an intra-arterial catheter. This is because with cuff inflation the reflected pressure waves summate, increasing systolic pressure, whereas the ischemic vasodilation downstream from the occluded cuff decreases cuff-opening diastolic pressure. Several noninvasive devices are commercially available that not only measure arterial pressure but also display the arterial waveform in real-time, allowing simultaneous calculations of CO, stroke volume, and variations in both arterial pulse pressure and stroke volume. These finger probe sensors degrade in the presence of severe vasoconstriction and the use of high-dose vasopressors but appear to be accurate during vasodilatory hypotensive states (eg, sepsis).

Invasive Measures of Arterial Pressure

Intra-arterial catheterization is the reference method for blood pressure measurement and should be used in all hemodynamically unstable patients in whom accurate and continuous measures of arterial pressure are required. The reason for this statement, which may be at odds with prior recommendations, is that intra-arterial catheterization provides instantaneous measures of MAP, arterial pulse pressure, and pulse pressure variation and estimation of CO with newer transducer technologies. The arterial catheter allows easily repeated blood sampling for chemistry studies and blood gas analysis. The most frequently used site for arterial catheterization is the radial artery. Femoral artery catheterization is also used and can be easier to perform in hypotensive patients, although it may

be associated with more complications. In the profoundly vasoconstricted patient, radial arterial pressure can underestimate central arterial pressure measured more proximally.

Arterial Pressure Targets

Once one measures arterial pressure, the major question is the target range of pressures to be maintained in order to sustain organ perfusion without excessively increasing LV afterload. Hypotension decreases organ perfusion pressure and blood flow, stimulating a sympathetic response to increase vasomotor tone, heart rate, and contractility. The change in local vasomotor tone in response to decreased arterial pressure forms the basis of autoregulation to maintain constant blood flow. The CO is important to sustain an adequate and changing blood flow to match changes in vasomotor tone such that arterial pressure to the organ remains optimal. Since CO is proportional to metabolic demand, there is no "normal" CO in the critically ill patient. However, as MAP decreases below 65 mm Hg in a previously nonhypertensive patient, organ perfusion becomes compromised. In previously hypertensive patients, targeting a MAP of 75 to 85 mm Hg results in less renal injury. Thus, a reasonable initial MAP target is 65 to 75 mm Hg, and this target is subsequently increased or decreased based on organ perfusion. To assess the adequacy of MAP to sustain peripheral perfusion, the bedside clinician needs to assess additional measures of organ perfusion, such as mixed venous O_2 saturation ($Sv{O_2}$), central venous O_2 saturation ($Scv{O_2}$), central venous $P{CO_2}$, lactic acid levels and their changes, sensorium, skin temperature, and urine output. Newer reginal blood flow measures and derived parameters exist and are being studied (discussed below), but their utility in assessing organ blood flow and monitoring response to resuscitation is not proven. Finally, individual organ perfusion is a function of MAP relative to its specific back pressure (**Table 1**).

Table 1. Perfusion Pressure for Different Organs (input pressure minus backpressure)

Organ	Inflow Pressure	Outflow Pressure (whichever is higher)	Perfusion Pressure
Brain	MAP	CVP or ICP	MAP – CVP or ICP
Heart	Diastolic BP	CVP or ITP	Diastolic BP – CVP or ITP
Kidney	MAP	CVP or IAP	MAP – CVP or IAP
Bowel	MAP	CVP or IAP	MAP – CVP or IAP

Abbreviations: BP, blood pressure; CVP, central venous pressure; ICP, intracranial pressure; IAP, intra-abdominal pressure; ITP, intrathoracic pressure; MAP, mean arterial pressure.

CENTRAL VENOUS PRESSURE

Although central venous access is often used as a secure site for infusion of fluids and vasoactive drugs as well as blood sampling, its utility in assessing intravascular volume status is poor. Central venous pressure (CVP) is not a measure of central blood volume nor can its values be used to determine whether a patient will be volume responsive. However, during spontaneous inspiration, decreases in CVP of greater than 2 mm Hg identify those patients who are volume responsive independent of the absolute CVP value, while increases in CVP reflect cor pulmonale (Kussmaul sign). Importantly, an increase in CVP during fluid infusion often reflects impending cor pulmonale and can be used as a stopping rule for fluid infusion.

Noninvasive Measures of Central Venous Pressure

CVP can be estimated noninvasively by inspection of jugular venous pulsation. With the patient sitting at 45°, the height of the jugular venous distention (JVD) above the sternal angle (itself about 5 cm above the center of the right atrium) can be used to estimate CVP. Potentially, this approach is most useful in documenting sustained increases in JVD or phasic increases in JVD with spontaneous inspiration, suggesting cor pulmonale or pulmonary hypertension, and periodic cannon waves seen in atrial fibrillation. Targeting fluid infusion to CVP goals of 8-12 mm Hg has been part of the Surviving Sepsis Campaign guidelines for many years and still persists in many therapeutic algorithms to guide fluid therapy in the critically ill. Importantly, this approach is being abandoned as being both inaccurate and often wrong in guiding fluid therapy. As discussed below, more functional measures have proven to be more sensitive and specific in assessing volume status and volume responsiveness.

Invasive Measures of Central Venous Pressure

Although CVP usually is measured from the internal jugular or subclavian vein via an indwelling catheter, CVP can be estimated from a femoral venous site as long as intra-abdominal hypertension is not present (ie, as long as the intra-abdominal pressure is <12 mm Hg), although use of the femoral site for a central venous catheter may be associated with a greater incidence of complications.

Since CVP will vary with changes in intrathoracic pressure (ITP), CVP is usually measured at end-expiration to minimize the confounding influence of changing ITP. In the dyspneic patient or a patient who is fighting the ventilator, finding a reliable end-expiratory CVP value may be impossible.

PULMONARY ARTERY PRESSURE AND PULMONARY ARTERY OCCLUSION PRESSURE

For more than 40 years, hemodynamic monitoring entailed bedside balloon flotation insertion of a pulmonary artery catheter (PAC) and subsequent measurement of CVP, pulmonary artery pressure, and pulmonary artery occlusion pressure (PAOP), plus determination of CO by thermodilution and of Svo_2 by reflectance oximetry. Although pulmonary artery pressure can be estimated by echocardiographic measures of tricuspid regurgitation, the accuracy of these measures is poor. In patients with pulmonary hypertension who need specific pulmonary vasodilatory therapy, PAC monitoring is essential. Its use in other conditions is of questionable utility compared with the use of less invasive monitoring options. PAOP can be measured by inflation of a PAC balloon and migration of the catheter tip into a medium-sized pulmonary artery, where the catheter tip is occluded. PAOP is used most often to assess pulmonary vascular resistance, determine the cause of pulmonary edema, estimate intravascular volume status and LV preload, and monitor LV performance.

Pulmonary Hypertension and Pulmonary Vascular Resistance

Sustained, increased pulmonary artery pressure impedes right ventricular ejection, causing right ventricular dilation, increases in CVP, and an obligatory decrease in CO. If pulmonary hypertension occurs rapidly, as occurs with massive pulmonary embolism or marked hyperinflation, acute cor pulmonale and cardiovascular collapse occur even though pulmonary artery pressure may not exceed 30 mm Hg. Pulmonary hypertension can be due to an increase in pulmonary vasomotor tone (eg, primary pulmonary hypertension), a pulmonary vascular obstruction (eg, pulmonary embolism), or passive increases in PAOP (eg, LV failure). Determining the cause of pulmonary hypertension is important because the treatment of each type is markedly different.

Pulmonary Edema

Pulmonary edema can be caused by elevations of pulmonary capillary pressure

(hydrostatic or secondary pulmonary edema), increased capillary or alveolar epithelial permeability (primary pulmonary edema), or a combination of both. If pulmonary capillary pressure increases above 20 mm Hg, hydrostatic vascular forces promote increased fluid flux across the capillary membrane, flooding the alveoli. The hydrostatic pressure required to induce pulmonary edema may be lower when plasma oncotic pressure is reduced, such as during severe hypoalbuminemic states. However, if capillary or alveolar cell injury is present, as in acute lung injury, alveolar flooding can occur at much lower pulmonary capillary pressures. Clinicians usually use PAOP as a surrogate of pulmonary capillary pressure, and if pulmonary venous resistance is not increased, this assumption is valid. However, persistently elevated pulmonary capillary pressures can coexist with normal PAOP values if pulmonary venous resistance and CO are both increased, as is often the case in high-altitude pulmonary edema and end-stage acute lung injury.

Left Ventricular Preload and Volume Status

PAOP is often erroneously used to assess intravascular volume status and LV preload. Regrettably, neither absolute PAOP values nor their change in response to fluid infusion trends preload or volume responsiveness. The reasons for this are multiple. First, although increases in LV end-diastolic volume will increase CO in volume-responsive patients, the relation between PAOP and LV end-diastolic volume is curvilinear, markedly affected by pericardial restraint, ventricular interdependence, and intrinsic myocardial diastolic compliance, all of which can change in a single heartbeat. The use of PAOP as a measure of LV end-diastolic volume and preload responsiveness is not recommended.

Assessment of Left Ventricular Performance

The assessment of LV performance is central to invasive hemodynamic monitoring. The primary determinants of LV performance are preload (LV end-diastolic volume), afterload (LV wall stress, which is itself the product of LV end-diastolic volume and diastolic arterial pressure), heart rate, and contractility. Since LV end-diastolic volume is a fundamental determinant of stroke volume and LV stroke work, PAOP is often used as a surrogate for LV end-diastolic volume and for the calculation of stroke work, which is the product of the difference between MAP to PAOP and stroke volume (i.e. LV stroke work = [MAP-PAOP]·SV). Thus, PAOP can be used to construct Starling curves that plot PAOP versus LV stroke work. With this approach, clinicians can classify

patients with heart failure by their PAOP and cardiac index values, using a PAOP of 18 mm Hg and a cardiac index of 2.2 L/min/m^2 as cutoff values. A low cardiac index with high PAOP reflects heart failure, and a low cardiac index with low PAOP reflects hypovolemia; in contrast, a high cardiac index with high PAOP reflects volume overload, and a high cardiac index with low PAOP reflects increased sympathetic tone. However, the normal LV response to increased demand is to increase intrinsic contractility, such that stroke volume will increase despite a decreasing LV end-diastolic volume and PAOP. Systolic heart failure is defined as a condition in which stroke volume can be increased only by the Starling mechanism. Thus, the use of this traditional “4-quadrant” method of analysis is less insightful during resuscitation from shock.

CARDIAC OUTPUT

A vast array of invasive and noninvasive devices are available that estimate CO accurately enough to drive clinical decision making, although each device has its own strengths and limitations. Accuracy and precision are often used to compare estimates of CO to PAC-derived thermodilution measures. Unfortunately, thermodilution, like all other indirect methods has its own inaccuracies, thus, there is no consensus method easily available to use as a gold standard for referencing device CO estimates. All CO estimating methods described below report CO estimates within 20% of reference values and are thus considered reliable enough for clinical decision making.

Noninvasive Measures of Cardiac Output

Reliable measurements of CO can be made noninvasively using a variety of techniques including ultrasound, plethysmographic pressure profile analysis, and bioreactance.

Echocardiography

The most commonly used noninvasive techniques to estimate CO are ultrasound based and include echocardiography, pulsed esophageal Doppler, and continuous-wave suprasternal notch ultrasound. Unfortunately, these techniques also have several limitations. They require training and attention to detail, and with the exception of esophageal Doppler probes for intubated patients, these techniques measure only one time point. However, they all reliably estimate CO. Threshold changes in aortic flow velocity during positive pressure ventilation may be used to predict volume responsiveness. Recent consensus conferences of

multiple professional societies have stated that basic expertise in ultrasound techniques should be a central part of all critical care training. However, since the transthoracic measures of CO are operator-dependent, single-time-point measures, they are used primarily to diagnose the causes of cardiovascular insufficiency and not to provide ongoing monitoring of resuscitation efforts.

Esophageal Doppler Ultrasound

Esophageal Doppler ultrasound uses an esophageal probe similar in size to a nasogastric tube to measure descending aortic flow as it parallels the esophagus. The probe is inserted orally or nasally to midthoracic level and rotated until the probe senses a characteristic aortic velocity signal profile. This technique can be taught to bedside nurses with minimal training and can be used to drive resuscitation algorithms to improve patient outcomes in patients undergoing high-risk surgery. A limitation of this technique is that nasogastric insertion is difficult and rarely used, thus, oral insertion is usually required. Accordingly, this is not the preferred technique in the awake nonintubated patient. Also, movement or migration of the probe can present a challenge to its use. However, complications with the use of esophageal Doppler measures are rare.

Transcutaneous Doppler Ultrasound

This modification of the esophageal Doppler technique uses a handheld probe placed at the suprasternal notch with the transducer aimed downward at the aortic valve. This technique is easy to learn and gives accurate measures of LV stroke volume and CO. Transcutaneous ultrasound will probably be most readily accepted in the emergency department, during medical transport, and on the general medical floor to rapidly identify cardiovascular instability.

Thoracic Electrical Bioreactance

Thoracic electrical bioimpedance has been in use for decades but is accurate only in highly shielded environments because electrical interference makes the measures of CO unreliable. However, using the frequency modulation component of the thoracic impedance signal, called *bioreactance*, markedly reduces this artifact and increases accuracy of the CO measurement. Bioreactance compares well with PAC thermodilution estimates of CO in patients during both cardiac surgery and trauma resuscitation.

Invasive Measures of Cardiac Output

Thermodilution Using the Pulmonary Artery Catheter

Invasive measurement of CO using the PAC remains the most common method used intraoperatively, although its use in the ICU is decreasing. The PAC has a thermistor located 4 cm from the tip and a proximal port located 30 cm from the tip. The clinician measures CO by using bolus injections and observing the thermal profile or semirandom intermittent thermal pulses from an upstream thermistor for continuous CO estimates. Importantly, measures of stroke volume and CO, when coupled with other measured hemodynamic variables, allow for the calculation of various parameters (eg, LV stroke work, pulmonary vascular resistance, Do_2, and O_2 consumption). Although the clinical utility and outcome benefit of pulmonary artery catheterization have been debated for many years, only a few studies have used PAC-specific measures to drive resuscitation algorithms and compare outcomes with those of other patients in whom this information is withheld. All of these studies showed outcome benefit.

Similar to the PAC is the transthoracic thermodilution method of estimating CO, which uses an arterial site to sense the thermal decay of a CVP injection site. This approach does not require PAC insertion but does require arterial flow-by, thus limiting arterial sampling to the femoral artery.

Arterial Pulse Pressure Waveform Analysis

Pulse pressure waveform analysis is considered minimally invasive monitoring because it requires only an arterial catheter. Several commercially available devices use proprietary algorithms that analyze various components of the arterial pressure waveform (or the pulse contour) to estimate CO. Each device estimates central arterial compliance differently, and techniques that require a standard external measure of CO for their calibration are the most accurate. Since arterial compliance varies depending on the patient's blood pressure, age, sex, and height, these devices require regular recalibration. The two common reference standards for calibration are transthoracic thermodilution and lithium dilution. Recent algorithms have been developed that do not require external calibration with a CO reference standard. Head-to-head comparisons of all of the invasive and minimally invasive devices routinely demonstrate significant intradevice variability, suggesting that if one uses these devices, it is best to stick with only 1 or 2 devices and learn to use them well rather than use several devices over time in the same patient. **Table 2** lists currently available monitoring devices, and several others are in development. In general, a minimally invasive device should be externally validated via independent means

if possible, and this should be done often if the cardiovascular tone of the patient varies rapidly.

Table 2. FDA-approved Commercially Available Devices to Estimate Cardiac Output at the Bedside (as of June 2016)

Noninvasive	
Transthoracic echocardiography	Various manufacturers
Transcutaneous ultrasound	USCOM (USCOM, Ltd, Australia)
Esophageal Doppler	CardioQ (Deltex, Ltd, UK)
Bioimpedance	BioZ (SonoSite, Inc, USA)
Bioreactance	NICOM (Cheetah Medical, Inc, USA)
Plethysmographic	Nexfin (Edwards Lifesciences, Inc, USA)
	CNAP (CNSystems, Inc, USA)/LiDCO Rapid (LiDCO, UK)
Tonometry	TL-200 (Tensys, Inc, Germany)
Invasive	
Minimally invasive (self-calibration)	Flotrac (Edwards Lifesciences, Inc, USA)
	LiDCO Rapid (LiDCO, Ltd, UK)
Minimally invasive (external calibration)	MostCare (PRAM Vyetech Health, Inc, Italy)
	PiCCO plus (Pulsion, Maquet, Ltd, USA)
	LiDCO Plus (LiDCO, Ltd, UK)
Pulmonary artery catheter	Bolus and continuous thermodilution (Edwards Lifesciences, Inc, USA)

ASSESSING VOLUME RESPONSIVENESS

Over the past 18 years, numerous studies have validated that either changes in arterial pulse pressure or stroke volume, referred to as pulse pressure variation (PPV) and stroke volume variation (SVV), respectively, induced by positive

pressure ventilation can accurately identify patients who are volume responsive and those who are not. A threshold value of greater than 15% for either PPV or SVV defines volume responsiveness when patients are ventilated with a tidal volume of 8 mL/kg or more. These parameters are not accurate during arrhythmias and spontaneous breathing because of varying R-R intervals and ventricular interdependence–induced changes in LV diastolic compliance, respectively. In those cases, one can perform a passive leg raising (PLR) maneuver and note the transient increase in CO. Importantly, although blood pressure may also increase during a PLR maneuver, it correlates poorly with the increase in CO. Postural changes such as PLR also transiently increase venous return and can be done in spontaneously breathing patients and those with arrhythmias. Starting with the patient in bed with the head of the bed elevated 30° to 45°, clinicians rotate the bed so that the patient's chest and head are supine and the legs elevated; this position is held for 1 minute while the maximal increase in CO is recorded. This maneuver approximates a 300-mL blood bolus in a 70-kg patient that persists for approximately 2 to 3 minutes. The dynamic increases in CO induced by PLR are as sensitive and specific in predicting volume responsiveness as is PPV during positive pressure mechanical ventilation using any of the commercially available, minimally invasive monitoring devices.

OXYGENATION AND TISSUE PERFUSION

CO varies with metabolic changes to match D_{O_2} with demand. Thus, there is no "normal" CO, only one that is adequate or inadequate to meet the metabolic demands of the body. Accordingly, measures of adequacy of organ perfusion indicate whether a specific CO value is appropriate. Adequacy of CO is determined by assessing end-organ function (eg, sensorium, urine output, skin temperature, and absences of mottling), arteriovenous O_2 content differences, serum lactate levels, and venoarterial P_{CO_2} differences. Importantly, maintenance of a normal blood pressure does not equate to adequate tissue blood flow because vasomotor tone varies to keep arterial pressure in an acceptable range, even when flow is inadequate.

Pulse Oximetry

Continuous monitoring of arterial blood O_2 saturation (Sa_{O_2}) via pulse oximetry is universally used in the ICU, although clinical data on its usefulness are lacking despite impressive clinical trials attempting to demonstrate a beneficial effect. The greatest utility of pulse oximetry is in reducing the need for repetitive

arterial blood gas analysis.

Detection of Hypoxemia

The most common use for oxygen saturation as measured by pulse oximetry (Spo_2) is the detection of hypoxemia. Hypoxemia is usually defined as an Spo_2 less than 90%. Titration of Fio_2 and other ventilatory maneuvers are used to keep Spo_2 greater than 90%, which is a common goal in most critically ill patients. However, increasing Spo_2 above 90% carries little additional benefit because the shape of the oxyhemoglobin dissociation curve limits oxygen-carrying capacity. Lower goals (ie, <90%) may be acceptable for patients with chronic lung diseases.

Detection of Volume Responsiveness

Another novel use of pulse oximetry is the plethysmographic waveform analysis. Variation in plethysmographic density from beat to beat reflects paired variations in arterial pulse pressure, thus making plethysmographic variability another method of assessing volume responsiveness in the ventilator-dependent patient, as discussed earlier.

Venous Oximetry and the Physiological Features of Svo_2 and $Scvo_2$

The Do_2 describes whole-body O_2 supply without reference to blood flow distribution or O_2 uptake. Do_2 is equal to the product of CO and arterial O_2 content (Cao_2). Cao_2 is the sum of O_2 bound to hemoglobin (Hb) (product of Hb concentration Sao_2) and dissolved O_2 which itself is a function of Pao_2). The formula is $Cao_2 = (Hb \times 1.36 \times Sao_2) + (Pao_2 \times 0.0031)$. Thus, dissolved O_2 in the plasma has minimal effect on overall Cao_2.

Clinically, Do_2 only has relevance to O_2 demand by whole-body O_2 consumption ($\dot{V}o_2$). In general, Do_2 and $\dot{V}o_2$ co-vary because it is the $\dot{V}o_2$ that drive CO, and it is CO that primarily determines Do_2. Since $\dot{V}o_2$ must equal the difference in Do_2 and the amount of O_2 remaining in mixed venous blood, $\dot{V}o_2$ can be expressed by the Fick principle as the product of CO and arterial to venous O_2 content (Cvo_2) difference ($Cao_2 - Cvo_2$): $\dot{V}o_2 = CO\ (Cao_2 - Cvo_2)$. Cvo_2 reflects the relationship between whole-body $\dot{V}o_2$ and CO under conditions of a constant Cao_2.

Venoarterial PCO_2 Differences as an Estimate of Circulatory Stress

The normal venoarterial PCO_2 difference is less than 5 mm Hg. If flow decreases, then for the same metabolic rate, venous PCO_2 will proportionally increase. Thus, a venoarterial PCO_2 difference greater than 7 mm Hg reflects either increased metabolic demand (eg, exercise, seizure) or inadequate DO_2 (eg, severe anemia, profound hypoxemia, or shock). The advantage of the venoarterial PCO_2 gradient over O_2 extraction is that the former is less affected by microcirculatory shunts or inadequate venous blood mixing because carbon dioxide is highly diffusible and equilibrates quickly.

FUNCTIONAL HEMODYNAMIC MONITORING

The primary utility of hemodynamic monitoring is to identify cardiovascular instability, determine causal factors, and guide therapy. A fundamental assumption underpinning these methods is that the rapid identification of tissue hypoperfusion and its correction will improve patient outcomes. Functional hemodynamic monitoring uses defined physiological perturbations to stress the cardiovascular system and reveal resultant changes in arterial pressure and CO. These methods include the assessment of volume responsiveness and the detection of occult tissue hypoperfusion.

Preload Responsiveness

The use of positive pressure breathing–induced PPV and SVV (discussed earlier) and PLR-induced changes in CO accurately predicts volume responsiveness. Other techniques also exist. The end-expiratory pause during positive pressure breathing maneuver notes increases in systolic arterial pressure and it presents by >10% reflect volume responsiveness. Similarly, ultrasound measures of inferior vena caval diameter variations during breathing also reflect volume responsiveness.

Goal-Directed Therapy

Initial studies performed in the 1980s suggested that the nonspecific increase in DO_2 to supranormal levels in critically ill patients improved survival. Subsequent studies using aggressive resuscitation to increase DO_2 to supranormal levels in patients with existing organ failure, in order to document survival benefit, reported that if anything, this practice increased mortality. However, early

aggressive resuscitation driven by hemodynamic monitoring—if done before the onset of organ injury—uniformly improves survival. These improved outcomes occur whether such resuscitation is performed as early goal-directed therapy in septic patients (with or without protocolized care), as preoptimization therapy for high-risk surgical patients, or as postoptimization therapy for postoperative patients with difficult intraoperative courses. Using a simple SVV minimization can markedly reduce intraoperative protocol hospital length of stay.

SUMMARY

Hemodynamic monitoring is performed to determine whether a subject is physiologically stable, to ascertain whether blood flow to the periphery is adequate to meet metabolic demands, to diagnose specific causes of circulatory shock, to determine the need for specific therapies, and to indicate when cardiorespiratory sufficiency has been reestablished. Using our knowledge of cardiorespiratory physiological changes, pathophysiological factors in disease, and the strengths and limitations of device measurement, bedside caregivers now have an extremely powerful array of monitoring devices to accomplish these goals. However, no hemodynamic monitoring device will improve outcome unless coupled with a treatment that itself improves outcome. What is primarily missing now is a field theory of global cardiorespiratory performance and validated management protocols that can be universally applied. Until these goals are accomplished, the need for well-trained, bedside applied physiologists in the guise of intensivists will remain a healthcare priority.

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CHAPTER 7

Cardiac Arrest and Resuscitation

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Key words: cardiac arrest, resuscitation

Cardiac arrest is an uncommon event in inpatient and outpatient settings, but due to poor outcomes, it remains 1 of the top 3 causes of death in the United States, accounting for approximately 300,000 deaths per year. Newer technologies and systems, such as automated external defibrillators (AEDs), rapid response teams, and changes to the basic life support (BLS) procedures, have been heavily promoted but carry equivocal evidence of improved outcomes. Although the techniques and tools of resuscitation for cardiac arrest have evolved, the overall goals remain the same: perfusion, oxygenation, treatment of the underlying cause, and prevention of recurrence.

CAUSES OF CARDIAC ARREST

Cardiac arrest is defined as sudden cessation of effective cardiac function. Cardiac arrest can be due to primary cardiac failure or can be an end manifestation of a myriad of heterogeneous medical conditions. Reported incidences vary based on age, gender, race, location of arrest (inpatient or outpatient), methods of identification and documentation, and availability of postmortem studies. Although coronary artery disease accounts for the majority of cases of cardiac arrest in both inpatient and outpatient settings, about one-third of cases of sudden death have noncardiac causes. Identification of the inciting causes, especially reversible causes of cardiac arrest, is necessary to determine the best therapeutic interventions as well as to guide systems development to decrease the incidence of cardiac arrest.

Presumed primary cardiac events are responsible for the majority of cardiac arrest cases, although true numbers are difficult to evaluate given the

unavailability of consistent, comprehensive postmortem data. Ventricular fibrillation (VF) is the most common cause of out-of-hospital cardiac arrests, accounting for 58% to 72% of outpatient arrests. VF is much less common in the inpatient setting, accounting for only 25% of inpatient arrests. However, incidences for both in-hospital and out-of-hospital cardiac arrests appear to be declining, for unclear reasons. Cardiac arrest due to hypoxia or asphyxia (most often from trauma, pulmonary embolism, drug overdose, acute on chronic respiratory failure, and unknown pulmonary failure) is less common than VF in the adult population. Trauma and injury are frequent causes of cardiac arrest, most commonly resulting from hemorrhagic shock, hypoxia and asphyxiation, or demand myocardial ischemia due to systemic hypoperfusion and less commonly resulting from a direct myocardial injury.

INPATIENT VERSUS OUTPATIENT CARDIAC ARREST

Chest compressions and artificial respiration have been the mainstays of cardiopulmonary resuscitation (CPR) since they were introduced in the 1960s. However, management strategies and outcomes following attempted resuscitation differ greatly between settings, such as an unwitnessed arrest with a first-aid responder versus a monitored arrest in a coronary care unit. The approach to patient management must be tailored to setting and available resources. After careful consideration, providers should direct treatment toward the most likely suspected cause of the arrest (**Table 1**).

Table 1. Common Causes of Cardiac Arrest

Cardiac disease

- Congenital heart disease
- Ischemic
- Arrhythmias
- Acute obstruction
- Fixed output states
- Valvular heart disease
- Cardiomyopathies
- Myocarditis
- Tamponade
- Sarcoidosis
- Trauma

Circulatory

- Hypovolemia
- Tension pneumothorax
- Pulmonary embolism

- Vagal reflex

Respiratory

- Hypoxia
- Hypercapnia

Metabolic

- Electrolyte abnormalities
- Hypothermia
- Circulating catecholamines

Drug effects/toxicity

Miscellaneous

- Electrocution
- Drowning

Information taken from Lim HS, Subbiah RN, Leong-Sit P, et al. How to diagnose the cause of sudden cardiac arrest. *Cardiol J.* 2011;18:210-216.

Outpatient Management of Cardiac Arrest

Cardiopulmonary Resuscitation

Algorithms such as the adult BLS system are targeted to untrained personnel in the out-of-hospital setting where an arrest occurs in an area with limited medical resources. CPR entails emergency support of the respiratory and circulatory systems, using chest compressions and artificial respiration.

Since its inception, CPR has been shown to improve survival in patients with cardiac and respiratory arrest. However, despite widespread promulgation to the general public, bystander-initiated CPR is still delivered in only 15% to 35% of cases. For patients who have out-of-hospital arrests, survival to discharge remains poor at 5% to 10%.

Current BLS guidelines have been updated to reflect the change in priority to a circulation-first from a ventilation-first approach. This change is based on the body of evidence in favor of maximizing chest compressions in CPR. Promotion of a compression-only approach is intended to improve bystander administration of CPR by simplifying the protocol and de-emphasizing the need for rescue

breaths, because it is well recognized that bystanders are averse to giving mouth-to-mouth rescue breaths. Initial data indicate that the compression-only approach results in increased rates of CPR administration and overall improved survival. Ewy et al showed an overall survival rate of 7.8% for patients receiving standard CPR versus 13.3% for patients receiving compression-only CPR in out-of-hospital cardiac arrests. Survival rates were 18% for patients with witnessed, shockable out-of-hospital cardiac arrests who received standard CPR versus 34% for those who received compression only CPR.

Automated External Defibrillators

The majority of outpatient arrests result from VF that can be reversed with early defibrillation, which has been shown to improve survival. AEDs have exploded in popularity in the out-of-hospital setting and are widely available in the majority of public settings in the US, including airports, shopping malls, schools, sports venues, and casinos. Use of AEDs in these settings has shown clear benefits in survival over use of CPR alone. Weaver et al showed an increase in survival to hospital discharge from 19% to 30% in patients who were treated by first responders with AEDs compared with patients who received defibrillation after paramedics arrived. In a similar study, O'Rourke et al examined the rollout of AEDs on airlines and found a 40% rate of survival to hospital discharge. Valenzuela et al examined the use of AEDs in casinos and found a 53% rate of survival to hospital discharge rate. Interestingly, in the study by Valenzuela et al, use of surveillance cameras allowed accurate recordings of the time from arrest to defibrillation. For those patients who experienced a witnessed cardiac arrest and received defibrillation no more than 3 minutes after arrest, survival to hospital discharge was 73%. Similar studies in children and young adults show that AED use increases survivability after cardiac arrest, and these findings support the installation of AEDs in schools and other public venues.

Inpatient Management of Cardiac Arrest

Cardiopulmonary Resuscitation

Overall survival of in-hospital cardiac arrest has remained largely unchanged over the last 40 years, ranging between 14% and 24.8%. Modest improvements recently seen likely reflect improved documentation and reporting, a more restrictive approach to the use of CPR in appropriate patient populations, and an increased use of do-not-resuscitate orders. Nonetheless, although overall survival

is low, almost 60% of those who do survive have good neurological recovery at the time of hospital discharge.

The cause of cardiac arrest in the inpatient environment is highly variable, which likely contributes to the lower success rates for resuscitation seen compared with the outpatient environment. VF is seen in only 25% of documented cardiac arrests. Inpatient cardiac arrest data also include those patients in the end stages of known cardiac disease who present with shock, respiratory failure, and apnea, leading to bradycardia, pulseless electrical activity, and asystole. These patients are less likely to respond to CPR and defibrillation and have poorer overall prognoses.

The enthusiasm for development of rapid response teams (also known as medical emergency teams or patient at-risk teams) stems from the observation that patients often exhibit signs of physiological deterioration prior to cardiopulmonary arrest (**Table 2**). Criteria for activation of these teams include threatened airway, apnea-tachypnea, tachycardia-bradycardia, hypotension, change in mental status, seizure, marked decreases in urine output, and concerns from physician, nurse, staff, or family. Indeed, implementation of these teams is 1 of the 6 recommendations set forth by the Institute for Healthcare Improvement's 100,000 Lives Campaign; however, data supporting the effectiveness of the team approach in reducing in-hospital deaths are lacking. A systematic review of the recent literature, including the recent MERIT trial, showed reductions of 17% to 65% in non–ICU-treated cardiopulmonary arrests and decreases in unplanned transfers to ICUs; however, overall hospital mortality rates were unchanged. Unfortunately, the evidence that exists is markedly heterogeneous, and further study with improved protocol design and standardization is needed. Success of these systems will depend on ongoing education, organizational support, meticulous data collection and review, and ongoing feedback.

Table 2. Immediate Preceding Causes of Cardiac Arrest

Cause	%
Arrhythmia	49
Acute respiratory insufficiency or compromise	37
Hypotension	32
Acute myocardial infarction or ischemia	10

Metabolic/electrolyte disturbance	10
Acute pulmonary edema	3
Acute pulmonary embolism	2
Airway obstruction	2
Toxicological problem	1

Adapted from Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation.* 2003;58:297-308.

Respiratory Management

Oxygen is the primary substrate for aerobic metabolism. Cellular oxygen consumption is dependent on adequate oxygen delivery, which in turn is dependent on hemoglobin concentration, arterial oxygen saturation, and cardiac output. Ensuring adequate cellular oxygenation and ventilation has remained a primary goal of all resuscitative algorithms for both adults and children. Therefore, maintaining a patent airway and ensuring adequate oxygenation and ventilation are the first priorities in managing any critically ill patient. Multiple devices are available to provide supplementary oxygen. All require an external oxygen supply that can be provided by either a cylinder or a wall unit.

Nasal cannula oxygen can be delivered at flow rates between 1 and 6 L/min, providing between 21% and 44% inspired oxygen content. A simple face mask can provide approximately 6 to 10 L/min and deliver oxygen concentrations between 35% and 60%. Face masks with an attached oxygen reservoir (nonrebreathers) can deliver between 6 and 15 L/min, providing 80% to 100% inspired oxygen content. A Venturi mask enables a more reliable and controlled delivery system for oxygen concentrations between 24% and 50%. The use of a Venturi mask is indicated in patients who retain carbon dioxide, including those with chronic obstructive pulmonary disease.

For patients who are unable to breathe spontaneously or who are unable to protect their airway, bag-valve-mask ventilation should be attempted. The bag-valve-mask device, which consists of a self-inflating bag and a nonrebreathing valve, provides positive pressure ventilation when used without an advanced airway. Bag-valve-mask ventilation is a challenging skill that requires significant practice for competency. Continued use of this device can produce gastric

insufflation, which may lead to vomiting and aspiration. When using a bag-valve-mask device, the clinician should insert an oropharyngeal airway to maintain the patient's airway. Patients should be bagged to achieve visible chest rise, which will deliver adequate tidal volumes. Although well-trained healthcare providers familiar with the bag-valve-mask ventilation technique can often achieve a leakproof seal between the mask and the face using one hand, it is often easier for two well-trained, experienced healthcare providers to work together, one of whom provides the leakproof seal between the mask and the face while gently lifting the patient's jaw while the second provider assists ventilation.

Advanced airway techniques can be used when spontaneous ventilation fails. The Combitube (Covidien-Nellcor and Puritan Bennett, Boulder, Colorado) is an invasive device with 2 inflatable balloon cuffs that is inserted without visualization of the vocal cords. Because the tube is more likely to enter the esophagus, the pharyngeal cuff is inflated and the patient is ventilated through the side openings adjacent to the vocal cords and the trachea. The Combitube should not be used in children younger than 16, in patients with a present gag reflex, in patients with suspected esophageal disease, or in patients who have ingested a caustic substance. Another advanced airway adjunct commonly used in the inpatient setting is the laryngeal mask airway (LMA). The LMA is composed of a tube with a cuffed, masklike projection at the end of the tube that is placed over the hypopharynx and then inflated. Cuff inflation pushes the mask against the tracheal opening, allowing air to flow through the tube and into the trachea. Both the Combitube and LMA are considered acceptable alternatives for advanced airway management.

Definitive airway stabilization is established via endotracheal intubation. The use of cricoid pressure can protect against regurgitation of gastric contents and facilitate placement of the endotracheal tube within the tracheal orifice. Cricoid pressure should be maintained until the endotracheal tube is successfully inserted, the cuff inflated, and appropriate tube placement confirmed. Appropriate endotracheal tube intubation should be confirmed by physical examination including the presence of bilateral breath sounds and the absence of breath sounds over the stomach. Additionally, capnography should be used to confirm placement.

During CPR, end-tidal CO_2 ($ETCO_2$) can be monitored, which is recommended to confirm placement and assess adequacy of compressions. Compressions

should be optimized to keep $ETCO_2$ levels greater than 20 mm Hg, suggesting adequate circulation to the lungs with effective CPR. Failure to maintain $ETCO_2$ greater than 10 mm Hg is an independent predictor of poor outcomes. If continuous waveform capnography is not available, an end-tidal colorimetric carbon dioxide indicator should be applied. A purple color indicates a lack of carbon dioxide and is consistent with esophageal intubation. Once appropriate placement of the endotracheal tube is ensured, bagged ventilation should be continued to ensure adequate chest rises as a surrogate for tidal volume delivery until a ventilator is available.

Administration of high-flow oxygen during resuscitation remains controversial. Increased Pao_2 (partial pressure of oxygen in arterial blood) during resuscitation may be associated with increased survival to hospital admission and improved neurological outcomes; therefore, administration of high-flow oxygen during resuscitation and CPR should be considered.

Access for Resuscitation

High-quality CPR and early defibrillation are the top priorities during the management of a cardiac arrest event. No drug given during resuscitation from a cardiac arrest has been clearly demonstrated to improve survival to hospital discharge or to improve neurological outcome. Therefore, drug administration is of secondary importance.

In the management of most patients with cardiac arrest, a peripheral IV line is preferable for drug and fluid administration. Ideally, this peripheral access should be established in a large vein, preferably an antecubital fossa. Once vascular access is established, either a saline lock or continuous infusion of isotonic fluid can begin. If infusion therapy is begun, the infusion rate needs to be at least 10 mL/h to keep the IV line open. Saline lock systems are particularly helpful in patients who have return of spontaneous circulation (ROSC) and require drug injections but not volume infusions. In patients who require volume infusion or resuscitation, a large-bore IV (generally a 14- or 16-gauge IV) should be established, again preferentially in the antecubital fossa or the forearm to facilitate rapid fluid administration.

Drugs administered during CPR typically need 1 to 2 minutes to reach the central circulation. Drug administration by bolus injection should be followed by a 20-mL bolus of IV fluids; if possible, the extremity in which the drug was administered should be elevated for 10 to 20 seconds to facilitate delivery of the

drug to the central circulation.

If IV access cannot be established, intraosseous (IO) access is the preferred type. IO cannulation provides access to the noncompressible venous plexus in the bone marrow and can be achieved within 30 to 60 seconds. This vascular access technique is suitable for patients of all age groups. The technique uses a rigid needle with a stylet to facilitate insertion. Insertion using a needle with a stylet is preferred to avoid clogging the needle device with bone marrow once access has been established. Although many sites are appropriate for IO infusion, the proximal tibia is particularly useful in all age groups. In general, the technique for insertion involves identifying the tibial tuberosity just below the knee joint. The insertion site is on the flat portion of the tibia approximately 1 to 2 finger breadths below and medial to this bony prominence. The needle should be inserted perpendicular to the tibia and often requires a twisting motion with gentle but firm pressure. The needle should be inserted through the cortical bone until there is a sudden release of resistance. Aspiration of bone marrow contents and blood into the hub of the needle confirms appropriate placement. A test infusion of saline should then be administered to ensure that the IO needle is truly in the marrow space. The presence of swelling at the insertion site following administration of the test dose of saline indicates that the needle is in an inappropriate position. If this occurs, the IO needle should be removed and the procedure attempted in a different bone to minimize the risk for fracture. Other appropriate IO insertion sites include the sternum, the distal tibia, the lateral or medial malleolus, the distal radius, and the distal ulna.

Dosing of medications is similar for both IV and IO administration. Administration of medications via the IO route should be followed with a 5- to 10-mL injection of normal saline to facilitate delivery into the central circulation. IO needles should not be inserted in areas of fracture or crush injuries. Additionally, in medical conditions that cause fragile bones, the use of IO needles should be avoided. The complications of IO needle infusions include fractures, compartment syndrome, and osteomyelitis. Careful insertion technique and attention to sterile technique minimize these complications. Many medical centers use specifically trained personnel for IO needle insertion, such as rapid response nurses or IV teams.

Central access is not needed during most resuscitation attempts. With ongoing CPR, establishment of central access can be difficult, particularly in the subclavian or internal jugular positions. However, central access is sometimes needed, and access to the common femoral vein is a viable option. This is also

an excellent site for placement of an introducer sheath should large-volume resuscitation be required, such as in cases of traumatic arrest or septic arrest. Insertion of a central line in a noncompressible area is a relative contraindication for patients who may subsequently require fibrinolytic therapy. In addition, the lack of sterility during placement of central lines in cardiopulmonary arrest situations should prompt early replacement of such lines once the patient is stabilized in a critical care unit.

Finally, drugs can be administered via the endotracheal route, although the absorption of drugs given by this route is unpredictable, and optimal dosing is unknown. A typical dose of drugs administered by the endotracheal route is about 2 to 2½ times the dose given by the IV route. All drugs should be diluted in 5 to 10 mL of either sterile water or normal saline, and then the drug should be injected directly into the endotracheal tube. This should be followed by several positive pressure breaths. The following medications can be administered via the endotracheal route for the management of cardiac arrest: atropine, vasopressin, epinephrine, and lidocaine. The mnemonic *NAVEL* is often used, where *N* stands for naloxone, which can be administered in patients with respiratory depression due to opiate ingestion.

Defibrillation

Use of the precordial thump, although part of the hallowed history of CPR, is associated with low efficacy. Several studies over the last 5 years show a 1.3% to 1.9% success rate, and this occurs only in patients presenting with ventricular tachycardia. However, given its relative safety, the precordial thump should be considered after a monitored cardiac arrest if a defibrillator is not immediately available.

Defibrillation is deliberate application of electrical current across the myocardium to induce depolarization and to reinitiate coordinated electrical activity. Modern defibrillators use biphasic waveforms, which have much higher rates of first shock success than older monophasic devices. Biphasic defibrillators are less susceptible to variations in transthoracic impedance and automatically adjust output to compensate.

The randomized controlled trial to compare fixed versus escalating energy regimes for biphasic waveform defibrillation (the BIPHASIC trial) compared fixed (150-150-150 J) versus escalating (200-300-360 J) current and found that conversion and fibrillation termination rates were greater in the escalating

current group in those patients requiring multiple shocks prior to successful cardioversion. Those patients requiring only a single shock were found to have equivalent rates of survival and of adverse effects as compared to those requiring multiple shocks. Data are lacking showing differences in outcomes between a strategy of immediate defibrillation versus delayed defibrillation after a course of CPR. Further study is mandated. Different manufacturers of defibrillators suggest different energy algorithms, so each resuscitation team must be educated concerning the protocols for the specific devices used.

Medications During Cardiopulmonary Resuscitation

For patients with pulseless electrical activity, epinephrine has been shown to improve rates of ROSC. Therefore, recommendations remain to give 1 mg of epinephrine every 3 to 5 minutes for patients in cardiac arrest. High-dose epinephrine has not been shown to be effective and therefore is not recommended. Vasopressin, lidocaine, procainamide, and magnesium sulfate all have been shown to be ineffective in the management of cardiac arrest. Only amiodarone has shown short-term benefits in survival, and therefore it remains the first-line alternative to epinephrine for shockable rhythms refractory to CPR, defibrillation, and vasopressor therapy. Magnesium sulfate is still recommended for the management of torsades de pointes and documented hypomagnesemia.

Hypothermia

Therapeutic hypothermia (TH), also referred to as therapeutic temperature management, has been shown in several randomized clinical trials to improve survival and neurological outcomes following out-of-hospital cardiac arrest. The 2 landmark studies were both published in 2002 in the *New England Journal of Medicine*. Bernard et al found a 49% rate of normal neurological function after cardiac arrest in patients receiving TH compared with 26% in patients not treated with hypothermia. Similarly, a multicenter European trial found a 55% rate of favorable neurological outcome in patients receiving hypothermia versus 39% in those without hypothermia. However, widespread implementation of this technology has been slow and is hampered by difficulties in training staff to use the protocols and techniques, and by concerns over adverse effects.

In the setting of cardiac arrest, TH is defined as the controlled lowering of core body temperature to 32°C to 36°C (89.6°F-96.8°F). Temperatures below this are difficult to manage because of shivering, which often requires significant sedation or neuromuscular blockade to control. A temperature below 32°C

decreases the threshold for cardiac arrhythmias such as slow atrial fibrillation (<31°C [87.8°F]) and VF (<28°C [82.4°F]).

International consensus guidelines for resuscitation have included TH since 2005. Guidelines by the American Heart Association recommend 12 to 24 hours of hypothermia when the initial rhythm is VF. However, the role of TH in non-VF arrest is unclear. In a recent retrospective observational study by Choi et al, TH was associated with better neurological outcome and higher survival to discharge in patients who experienced out-of-hospital cardiac arrest with pulseless electrical activity as their presenting electrocardiographic rhythm. Further study is needed to determine the role of TH in this population. In-hospital cardiac arrests, which have declined with the implementation of medical emergency response teams, are less frequently VF arrests and may have fewer indications for the use of TH. However, the availability of personnel and resources makes early implementation of TH more feasible, and clinicians need to carefully balance the risks of TH with the potential for improved neurological outcome after injury from cardiac arrest. Indications for use of TH in situations such as pediatric cardiac arrest and respiratory arrest leading to cardiac arrest have been poorly studied to date, and TH cannot be recommended in these cases.

Various techniques for inducing hypothermia are under study. Original protocols entailed refrigerated cooling blankets and ice packs. Newer systems include more efficient surface cooling pads, jackets, and helmets; intravascular cooling systems via an inferior vena cava temperature exchange catheter or large-volume, ice-cold crystalloid fluid infusion; and targeted cerebral cooling via the nasopharyngeal approach. Large-volume, ice-cold crystalloid fluid in particular appears to be a promising approach that minimizes cost, complexity, and time to initiation of TH.

SPECIAL POPULATIONS

The Pregnant Patient

Cardiac arrest during pregnancy is rare (1 in 30,000 pregnancies) but increasing in frequency. Increased age at the time of pregnancy, coupled with a rise in the incidence of obesity, puts women at increased risk for ischemic cardiac disease. Additionally, patients with congenital heart defects are increasingly surviving to childbearing years and thus have an increased likelihood of becoming pregnant. Causes of cardiac arrest during pregnancy include hemorrhage, preeclampsia,

HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), amniotic fluid embolism, pulmonary embolism, sepsis, trauma, and anesthetic complications. Given low numbers of subjects, no large, randomized controlled trials have evaluated different management techniques in the pregnant patient with cardiac arrest, and so guidelines for resuscitation are based on recommendations and data from small, observational studies.

The best treatment to support the fetus is effective resuscitation of the mother. During a normal pregnancy, cardiac output is increased by 1.0 to 1.5 L/min. Systolic blood pressures tend to be 10 to 15 mm Hg lower. Hematocrit concentration is decreased due to increased plasma volume, leading to physiological anemia of pregnancy. To accommodate an increased oxygen consumption of approximately 20%, tidal volume is increased, and there is a decrease in functional residual capacity.

Resuscitation therefore must address these physiological changes of pregnancy. The airway must be carefully monitored and secured expediently as needed. Fluid resuscitation must be adjusted for the increased plasma volume of pregnancy. Current drug and medication recommendations are not altered in the pregnant patient. Transthoracic impedance is not altered during pregnancy, and current energy settings for defibrillation are unchanged for the pregnant patient. The gravid uterus can cause aortocaval compression that can compromise the venous return of the mother and lead to hemodynamic compromise of the mother and fetus. A left lateral tilt of 15° to 30° is recommended to shift the gravid uterus off the inferior vena cava. Chest compressions can be effectively applied in the maximal 27° left lateral tilt position (such as with use of the Cardiff wedge) and will produce 80% of the force applied in the supine position. Diligent evaluation of the effectiveness of chest compressions is very important during resuscitation of the pregnant patient.

Perimortem cesarean delivery (PMCD) is recommended only within 4 to 5 minutes of onset of maternal cardiac arrest. However, case series and retrospective cohort studies suggest that good outcomes are possible even after this 5-minute interval, especially at older gestational ages (30-38 weeks). Multiple case reports of PMCD document babies born without sequelae and report ROSC in the mother after evacuation of the uterus. Therefore, if ROSC does not occur in the first 4 minutes after maternal cardiac arrest, PMCD should be considered when all other resuscitation methods fail. Consideration of PMCD for fetuses below an estimated gestational age of 28 weeks must take into account the available resources of the institution and the experience of providers.

Pediatric Cardiac Arrest

Causes for cardiac arrest in the pediatric population differ from those in adults, but outcomes remain poor. In the inpatient setting, most children regain spontaneous circulation and more than 25% survive to discharge. In contrast, only 10% survive to discharge when cardiac arrest occurs out of hospital. Explanations for this include difficulties in performing effective CPR in pediatric patients and differing pathogenesis of cardiac arrest. Coronary artery disease with VF leading to cardiac arrest is rare in children. Cardiac arrest in these patients is more likely unwitnessed, is of prolonged course, and most commonly results from respiratory arrest due to hypoxia or asphyxia or due to circulatory shock and arrest. These factors underlie the rationale for prolonged immediate CPR prior to notification of emergency medical services and prior to use of AED. Defibrillation is the treatment of choice for VF or pulseless ventricular tachycardia, although the optimal current is unknown. Initial settings of 2 J/kg and subsequent settings of 4 J/kg are generally recommended.

It seems logical that outcomes in pediatric cardiac arrest, as in adult cardiac arrest, are related to whether events are witnessed, whether bystander CPR is performed, and the time elapsed to CPR and arrival of emergency medical services; however, data in pediatrics are limited. Cardiac arrest associated with rapid onset of hypothermia or icy water immersion can have good neurological outcomes in pediatric patients despite prolonged (>30 minutes) duration of arrest. Arrests associated with blunt trauma and septic shock have uniformly poor outcomes in pediatric patients.

OUTCOMES

Outcomes in cardiac arrest vary widely between different causes of arrest and the settings in which arrest occurs. Other factors that influence outcome include recognition time, response time of trained personnel, type of cardiac dysrhythmia, and timeliness of chest compressions. Unfortunately, only 15% to 35% of patients receive timely, effective CPR in the out-of-hospital setting, and survival to discharge ranges from 5% to 10%. For every minute that CPR is delayed, a patient's chance of survival decreases by 7% to 10%.

Significant determinants of outcome include initial rhythm, concurrent cardiac and noncardiac comorbid conditions, and time of day when cardiac arrest occurs. Specific patient factors associated with poor survival include a history of diabetes, pulseless electrical activity or asystole as the initially recognized

rhythm, cardiac arrest during the night, metastatic disease, impaired renal function, and dependent functional status. Male gender, compared with female gender, is associated with a higher 1-month survival rate but with similar overall survival rates and poorer overall neurological outcomes. Black patients appear to have lower rates of survival, although whether this is attributable to less frequent use of do-not-resuscitate orders remains unclear.

SUMMARY

Survival following cardiac arrest, whether it initiates in or out of the hospital, depends on high-quality chest compressions, immediate electrical therapy for shockable rhythms, and appropriate airway support. Following algorithm-defined therapies, such as advanced cardiac life support and BLS guidelines, offers the patient's best chance for ROSC and, ultimately, hospital discharge. Immediate response teams for in-hospital cardiopulmonary arrests may improve ROSC, and newer technologies that identify patients at highest risk for arrest may allow earlier interventions to prevent those arrests.

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CHAPTER 8

Severe Heart Failure, Cardiogenic Shock, and Pericardial Tamponade (Including Principles of Intra-aortic Balloon Pumps and Ventricular Assist Devices)

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Key words: cardiogenic shock, inotrope, intra-aortic balloon pump, ventricular assist device

Severe heart failure, cardiogenic shock (CS), and pericardial tamponade are life-threatening conditions, constituting the most severe forms of acute heart failure (AHF). In contrast to patients with chronic heart failure, patients with AHF have recourse to very few effective treatments to improve clinical outcomes. This is paralleled by the lack of large randomized trials in this setting over the last 2 decades. More recently, guidelines have become available to address the management of AHF,[1] and surveys and registries have generated important information concerning the clinical characteristics and prognoses of patients with AHF syndrome (including CS).

EPIDEMIOLOGICAL CHARACTERISTICS OF CARDIOGENIC SHOCK

The main cause of CS is ischemic cardiomyopathy. Mortality rates for CS vary from 25% to 60%.[2-5] Moreover, CS remains the leading cause of death in patients hospitalized with acute myocardial infarction (AMI) that is complicated by CS.[6] **Table 1** synthesizes reported incidence and management of CS in heart failure.

The main causes of in-hospital death in patients with CS complicating AMI have been reported by the registry of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, ventricular

septal rupture was associated with 87.3% in-hospital mortality, predominant left ventricular failure with 59.2%, mitral regurgitation with 55.1%, right ventricular failure with 55.0% and tamponade also with 55.0%.[2] Ventricular septal rupture carried the highest mortality (87.3%), whereas patients with predominant left ventricular (LV) failure had a mortality rate of 59.2%.

Table 1. Reported Incidence and Management of Cardiogenic Shock in Heart Failure Registries

Registry	Sample Size	Type of Patients	Incidence of CS, %	In-Hospital Mortality Rate of CS, %	Use of IABP, %	Use of LVAD, %	Use of IV Inotropes, %
ALARM-HF[46]	4,953	All patients with AHF	11.7	NR	4.8	NR	39
EuroHeart Failure survey[3,47]	11,327	Chronic HF and AHF	<1[a]	NR	NR	NR	7.2
EFICA[5]	599	All patients with AHF admitted to CCU/ICU	29	58	NR	NR	53
Italian survey[4]	2,807	All patients with AHF	7.7	25	1.2	NR	24.6
OPTIMIZE-HF[48]	48,612	Chronic HF and AHF	NR	NR	NR	NR	7
SHOCK Trial Registry[2]	1,190	CS complicating acute MI	100	60	53	0.8[b]	70.1
EHFS-II[49]	3,580	All patients with AHF	4	40	2.2[c]	NR	10.2[d] (dobutamine only)
ADHERE[26]	105,388	Chronic HF and AHF	NR	NR	<1[e]	NR	NR

Abbreviations: AHF, acute heart failure; CCU, cardiac care unit; HF, heart failure; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MI, myocardial infarction; NR, not reported; SC, cardiogenic shock.

[a]Thirty-two percent of men but only 15% of women had left ventricular systolic dysfunction reported as severe.

[b]Value is based on 856 patients with available data.

[c]Value corresponds to 30.9% of patients with cardiogenic shock.

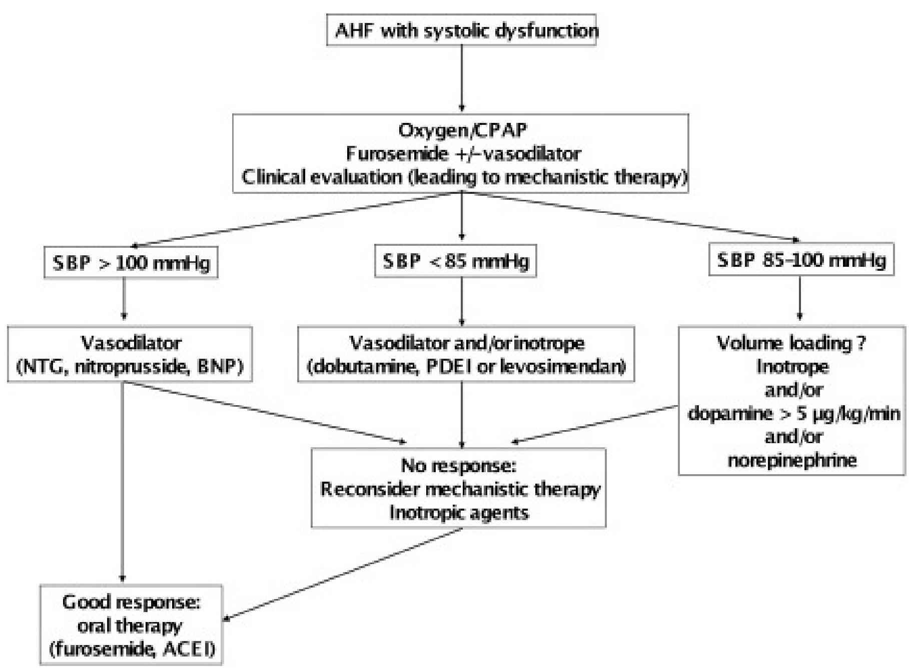
[d]Value corresponds to 44.6% of patients with cardiogenic shock.

[e]Value corresponds to 2% among the 19,754 patients admitted to CCU/ICU.

INOTROPES FOR SEVERE HEART FAILURE

In theory, inotropic agents can improve hemodynamic parameters by increasing cardiac output and reducing left and right ventricular filling pressures. **Figure 1** depicts the rationale for using inotropic agents in AHF, as reported in the 2005 European Society of Cardiology (ESC) guidelines.[1] Inotropic agents are indicated in the presence of peripheral hypoperfusion (hypotension and decreased renal function) with or without congestion and in cases of pulmonary edema refractory to diuretics and vasodilators at optimal dose (class IIa recommendation; level of evidence: C). Despite the potential hemodynamic benefits and ability to improve mitochondrial function of noninfarcted myocardium, inotropes increase oxygen demand in a failing heart with limited supply and therefore may provoke arrhythmias and lead to cellular disruption and necrosis.[7-9] Moreover, the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)[10] registry suggests that the use of inotropic agents in AHF syndromes may increase mortality regardless of the patient's severity of disease. Thus, the lowest effective dose of inotropes should be used in CS.[11]

Figure 1. Rationale for use of inotropic drugs in acute heart failure



Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; BNP, brain natriuretic peptide; CPAP, continuous positive airway pressure; NTG, nitroglycerine; PDEI, phosphodiesterase inhibitor; SBP, systolic blood pressure.

Adapted from Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J.* 2005; 26(4):384-416. By permission of Oxford University Press.

In a recent meta-analysis of individual data, Pirracchio et al[12] suggested that in the most severe forms of CS where a vasopressor is immediately required, adding an inodilator may improve short-term mortality. It is increasingly suggested that dopamine should be avoided in patients with CS.[13,14] Only one small observational study showed that administration of vasopressin in patients with CS due to AMI increased mean arterial pressure without a negative impact on cardiac output.[15] Levosimendan could be of interest for patients with CS,[16-19] but further study is needed. The phosphodiesterase inhibitors enoximone and milrinone have been shown to increase cardiac index in patients with CS, but no data are available supporting superiority of these agents in comparison to catecholamines.

Of note, the updated ESC guidelines[20] do not recommend vasopressors (norepinephrine) as first-line agents except in the case of CS when the combination of an inotropic agent and fluid challenge fails to restore the systolic blood pressure to more than 90 mm Hg and organ perfusion is inadequate despite an improvement in cardiac output. In the latter situation, norepinephrine is preferred over dopamine. The guidelines indicate that intravenous inotropic agents (dobutamine) may be considered to increase cardiac output. Patients with sepsis complicating AHF may require vasopressors. Because systemic vascular resistance is usually high in cases of CS, all vasopressors should be used with caution and discontinued as soon as possible.

REVASCULARIZATION IN CARDIOGENIC SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION

Over the last 2 decades, the morbidity and short-term mortality of AMI have been substantially reduced by the use of reperfusion therapy. However, CS remains the leading cause of death in patients hospitalized with AMI.[6] Several controlled trials have attempted to resolve the issue of revascularization in CS complicating AMI. The SHOCK trial demonstrated that in patients with CS, emergency revascularization did not significantly reduce overall mortality at 30 days; however, after 6 months a significant survival benefit was noted. This

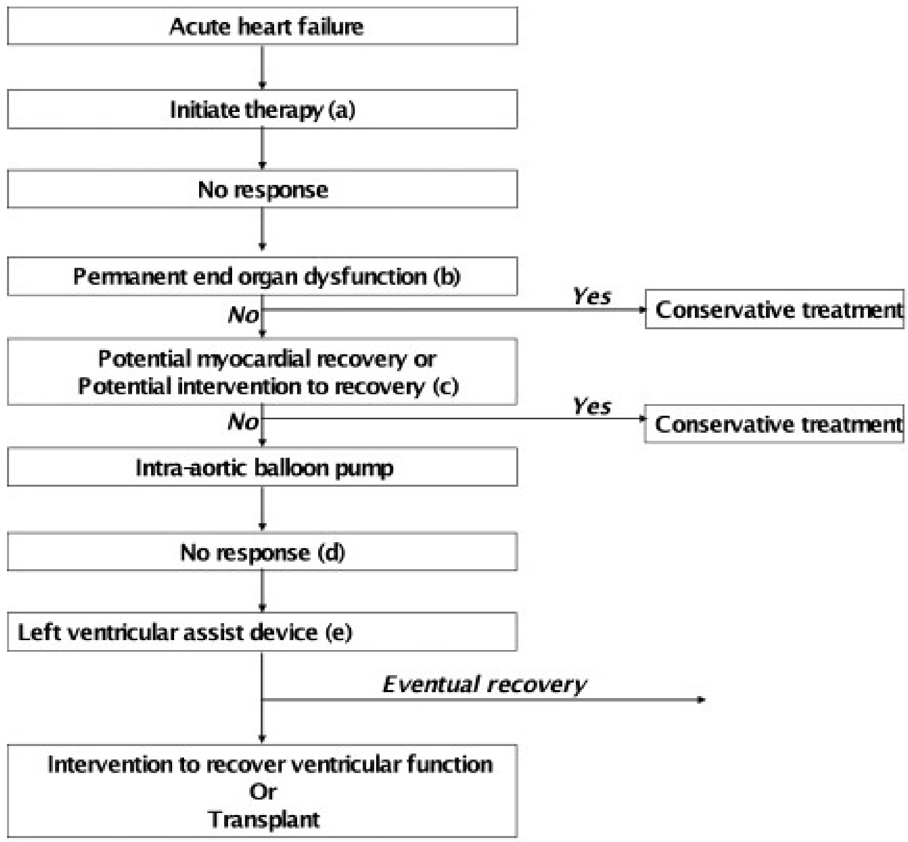
finding led the authors to recommend early revascularization for patients with AMI complicated by CS.[21] A follow-up study of the patients included in the SHOCK trial showed that a strategy of early revascularization resulted in a 13.2% absolute and a 67% relative improvement in 6-year survival compared with initial medical stabilization.[22] Another article reported results from the National Registry of Myocardial Infarction (NRMI) in the United States.[6] The study showed that among 293,633 patients included in the registry, CS occurred in 2.3% of patients younger than 75 years and in 3.1% of those 75 years or older. In this study, the use of percutaneous coronary intervention for patients with CS was independently associated with a lower risk of in-hospital mortality (adjusted odd ratios at 0.54 with 95% confidence interval at 0.47-0.60).

DEVICE THERAPY

Recent guidelines and experts recommendations[20,45] state that temporary circulatory assistance may be indicated (1) in patients with AHF who are not responding to conventional therapy and who have potential for myocardial recovery or (2) as a bridge to heart transplant or interventions that may result in significant recovery of heart function (class IIb recommendation; level of evidence: B).

Early mechanical device therapy may be useful in patients who have not responded to other therapies during the first 6 to 12 hours after presentation. Patients who may be candidates for device therapy include those with severe and persistent hypotension or hypoperfusion despite the use of inotropes, urine output less than 30 mL/h, decreasing oxygen saturation, persistent ischemia, or cold or mottled skin. **Figure 2** depicts the selection of candidates for LV assist devices as proposed by the 2005 ESC guidelines[1] and the 2008 updated guidelines.[24] Moreover, expert opinion indicates that device therapy should be applied as soon as needed to lessen tissue hypoperfusion and to avoid the potential detrimental effect of catecholamines.[25] Two categories of devices are available: intra-aortic balloon pumps (IABPs) and ventricular assist devices (VADs), the latter of which include extracorporeal circulatory assistance.

Figure 2. Selection of candidates for left ventricular assist devices



(a) No response to conventional treatment of acute heart failure, including appropriate use of diuretics and fluids, intravenous inotropes, and vasodilators. (b) End-organ dysfunction, including severe systemic disease, severe renal failure, pulmonary disease, hepatic dysfunction, and permanent central nervous system injury. (c) Potential recovery of myocardial function or cardiac function: for example, acute myocardial ischemia, postcardiotomy shock, acute myocarditis, acute valvular heart disease, or candidate to heart transplant. (d) Absence of clinical improvement after intra-aortic balloon pump and mechanical ventilation. (e) Final indication may depend on availability of device and experience of cardiovascular team.

Adapted from Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005; 26(4):384-416. By permission of Oxford University Press.

Intra-aortic Balloon Pumps

Considered the first-line device, an IABP can be placed rapidly in the cardiac catheterization laboratory or in the cardiac care unit or ICU. Use of an IABP improves coronary and peripheral perfusion via diastolic balloon inflation and augments LV performance via systolic balloon deflation with an acute decrease in afterload. The incidence of IABP use for AHF varies among the registries, from less than 1% to as much as 53%, as described in **Table 1**. Data from the Acute Decompensated Heart Failure National Registry (ADHERE)[26] indicate

that less than 1% of patients hospitalized for AHF syndrome receive an IABP during the entire hospital stay; thus, the utility of the IABP during early AHF is relatively low and should be further defined. In the SHOCK trial registry, lower in-hospital mortality was observed in patients treated with IABP support, particularly when combined with thrombolysis or early revascularization.[27] A similar trend was observed in a large database of patients presenting with AMI; in-hospital mortality was lower (49%) in patients treated with IABP support than in those treated without it (67%).[28]

The most common indication for IABP is in the postoperative period of coronary artery bypass grafting. A 2011 Cochrane review[29] stated that the IABP is integral to current postoperative management and is of undeniable efficacy, so it is not surprising that there have been no randomized controlled trials (RCTs) in this setting, as ethical permission would not be forthcoming. Within current clinical practice, the IABP is deployed preoperatively in a number of circumstances including unstable angina refractory to medical treatment and CS following coronary intervention.[30] The Cochrane review also suggested that the IABP may be beneficial in terms of survival following the operation; however, the review pointed out many problems concerning the validity of the trials reviewed and concluded that a categorical answer to this question requires further RCTs. Despite the potential benefits in perioperative support, the most recent guidelines clearly indicate that IABP is not routinely recommended in CS.[20]

Ventricular Assist Devices

There are 5 possible indications for VAD insertion: bridge to decision, bridge to candidacy, bridge to cardiac transplantation, bridge to recovery, and destination therapy.[24,31]

Interestingly, left VADs (LVADs) allow partial or total support of the systemic circulation in cases of severe LV failure, whereas IABPs only decrease the preload and the afterload. Along with allowing the recovery of normal hemodynamic parameters, LVADs reduce ventricular strain and promote remodeling and thus may have beneficial effects on long-term outcome.

LVADs are not generally used within the first 6 to 12 hours. However, VADs should be considered earlier rather than later, before end-organ dysfunction is evident. Types of LVADs are described in **Table 2**. Several reviews have detailed the characteristics, advantages, and risks associated with specific LVADs.[32-35] A meta-analysis of controlled trials compared percutaneous LVAD versus IABP for

the treatment of CS.[36] Three trials[37-39] including 100 patients were included in the meta-analysis. The conclusion was that although the percutaneous LVAD provides superior hemodynamic support compared with IABP in patients with CS, the use of these more powerful devices did not improve early survival (relative risk for 30-day mortality 1.06; 95% confidence interval, 0.68-1.66). Research results do not yet support percutaneous LVAD as the first choice in the mechanical management of CS, but larger RCTs using the most recent devices are needed to address this issue. The recent recommendations[20] propose to implant LVADs in patients with more than 2 months of severe symptoms despite optimal medical and device therapy and more than 1 of the following: (1) LVEF less than 25% and, if measured, peak $\dot{V}O_2$ less than 12 mL/kg/min; (2) 3 or more hospitalizations for heart failure in the previous 12 months without an obvious precipitating cause; (3) dependence on IV inotropic therapy; (4) progressive end-organ dysfunction (worsening renal and/or hepatic pressure: pulmonary capillary wedge pressure ≥20 mm Hg and systolic blood pressure ≤80-90 mm Hg or cardiac index ≤2 L/min/m^2); (5) absence of severe right ventricular dysfunction together with severe tricuspid regurgitation.

No evidence is available to guide the choice between surgically implanted versus percutaneous VADs. In a 2008 review, Cook and Windecker[33] reported that the average 30-day survival rates of patients receiving VADs for CS due to AMI were 49% and 85% for surgically implanted versus percutaneous VADs, respectively. However, these results came from an observational study, and no RCT results support this difference. Recent data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) led to determine which type of mechanical support patients with advanced heart failure need.[40]

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is performed percutaneously and is increasingly used for temporary mechanical circulatory support given the relatively low cost of the system and disposables as well as its broad availability (**Table 2**). ECMO is a simplified cardiopulmonary bypass using a centrifugal pump (5-6 L/min), allowing for augmentation of venous drainage despite relatively small cannulas and providing the option of taking over the full workload from the heart. There are several indications for ECMO, including intraoperative or perioperative low cardiac output syndrome, severe AMI, and cardiac resuscitation (all of which are types of ventricular failure). Another advantage is that ECMO can be useful in cases of associated respiratory failure

and even as a renal support by addition of a hemofilter.[25] The limitations of ECMO mainly stem from the necessity of permanent operator supervision and intervention and its relatively limited length of use (30 days).

Table 2. Left Ventricular Assist Devices

	Principle	**Characteristics**	**Clinical Uses**	**Complications**
Percutaneous devices				
Tandem Heart (Cardiac Assist Inc, Pittsburgh, Pennsylvania, USA)	Two cannulas: inflow cannula placed via the femoral vein into the atrium by a transseptal puncture approach and outflow cannula in the femoral artery.	Can generate flow up to 5 L/min.	Successfully used for high - risk percutaneous interventions, for postcardiotomy heart failure, bridge-to-bridge device, and as a bridge to transplantation.[36,50-54]	
Impella Recover LP2.5 and LP5.0 (Abiomed Europe, Aachen, Germany)	Placement via the femoral artery.	Can generate flow of 2.5 L/min (Impella 2.5) or 5 L/min (Impella 5.0).	Used successfully during high - risk coronary angioplasty and for patients with cardiogenic shock caused by MI.[38,55] Used to treat AHF due to cardiac allograft rejection.[56,57]	Lower - extremity ischemia and cannula dislodgement.
Extracorporeal membrane oxygenation	Two cannulas: one for the inflow, the other for the outflow. Performed percutaneously using femoral access.	Incorporates an oxygenator into the circuit.	Useful in patients with both heart failure and an inability to adequately oxygenate the blood.	Bleeding and distal leg ischemia.[58-61]
Surgically implanted devices				
First-generation VADs —PVAD (Thoractec Corporation, Pleasanton, California, USA)	Pulsatile flow via large pericorporeal consoles. Device inserted via a traditional sternotomy.	Can generate cardiac output between 5 and 7 L/min.	Mainly used as bridge to transplant or bridge to recovery.	High risk of infections and bleeding. Perioperative mortality rate is 15%-20%, and overall survival until device

—BVS 5000/AB5000 (Abiomed Corporation, Danvers, Massachussets, USA)				explanation is 60%-70%.
Second - generation VADs —HeartMate IP/XVE LVAS (Thoratec) —Novacor (WorldHeart Corporation, Salt Lake City, Utah, USA) —ArrowLionHeart (Arrow International, Reading, Pennsylvania, USA)	Device inserted via a traditional sternotomy.	Can generate cardiac output between 5 and 7 L/min.	Mainly used as bridge to transplant or bridge to recovery. Sometimes used as destination therapy.	Improved patient mobility leading to decreased infection rates and neurocognitive complications. 31
Third - generation VADs —HeartMate II (Thoratec) —Jarvik 2000 FlowMaker (Jarvik Heart, New York, New York, USA) —MicroMed Debakey Pump (Micromed Inc, Houston, Texas, USA) —IVAD (Thoratec) —Berlin Incor (Berlin Heart,	Fully implantable, axial flow impeller pumps with lack of percutaneous lines and implantation within the pericardium, obviating a need for a pump pocket.	Can generate cardiac output up to 7 L/min.	Used as destination therapy.	Decrease in complications, specifically infections.

The Woodlands, Texas, USA)				

Abbreviations: AHF, acute heart failure; AMI, acute myocardial infarction; LVAD, left ventricular assist device; MI, myocardial infarction; VAD, ventricular assist device.

PERICARDIAL TAMPONADE

Pericardial tamponade is compression of the heart due to the pericardial accumulation of liquid, which can be fluid, pus, blood, clots, or gas. The cause could be effusion, trauma, or rupture of the heart.[41] The management of pericardial tamponade includes symptom management and treatment of the underlying cause. Thus, prompt identification of the cause is critical.

A key diagnostic finding of cardiac tamponade is pulsus paradoxus, conventionally defined as an inspiratory systolic decrease in arterial pressure of 10 mm Hg or more during normal breathing. However, pulsus paradoxus is not always present; for example, it could be absent in cases of severe hypotension.

Electrocardiogram usually shows signs of pericarditis, but the only quasi-specific sign of tamponade is electrical alternation.[42] Echocardiography is the principal tool for diagnosing pericardial effusion and cardiac tamponade. Among echocardiographic signs, the most characteristic (although not entirely specific) is chamber collapse, almost always of the right atrium and ventricle.

The treatment of cardiac tamponade is drainage of the pericardial contents, preferably by needle pericardiocentesis with the use of echocardiography.[43] Surgical drainage is preferable in case of intrapericardial bleeding, clotted hemopericardium, or thoracic conditions that make needle drainage difficult or ineffective.[44] The goal of drainage is to relieve compression and not to entirely empty the pericardial space, which could be deleterious because of the risk of myocardial injury.

SUMMARY

AHF, especially secondary to CS and pericardial tamponade, represents a complex and challenging situation affecting a heterogeneous population at high risk of short-term morbidity and mortality. Diagnosis should be made early, and goal-directed treatment strategies should be initiated promptly to attain the best outcomes.

Although CS represents the most severe form of AHF, as for all other clinical scenarios, a multidisciplinary approach along the entire patient journey from prehospital care to hospital discharge is needed to ensure early recognition, risk stratification, and the benefit of available therapies.[45]

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CHAPTER 9

Sepsis and Septic Shock: Epidemiology, Pathophysiology, Diagnosis, and Management

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Key words: sepsis, septic shock, pathophysiology, goal-directed therapy, corticosteroids, activated protein C

More than a million Americans are hospitalized for sepsis annually, it is the ninth leading cause of death, and it is the most common cause of death among critically ill patients in noncoronary ICUs. The US Centers for Disease Control and Prevention estimates the annual cost of hospital care for sepsis to be more than $14 billion per year in the United States. Thus, sepsis is an important public health problem.

DEFINITIONS

The definitions of sepsis and septic shock have evolved over the past 25 years. In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine held the first Consensus Conference – 'Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis' and proposed a broad framework to define systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis. These conditions were envisioned as a continuum of worsening inflammation, starting with SIRS and evolving from sepsis to severe sepsis and ultimately septic shock. The criteria for SIRS were based on temperature, heart rate, respiratory rate, and white blood cell count. The definition of SIRS required at least 2 of the 4 criteria to be met. SIRS often occurs in the setting of infection, but noninfectious conditions, such as burns, acute pancreatitis, and trauma, could lead to SIRS as well. Sepsis was defined as the presence of SIRS and a source of infection, whether proven or suspected. Severe sepsis was defined as sepsis accompanied by organ dysfunction.

Although the 1991 Consensus Conference laid the framework to define sepsis, it had important limitations. The “2 out of 4” criteria for SIRS and the thresholds were somewhat arbitrary and not specific to sepsis alone. The criteria did not include biochemical markers, such as C-reactive protein, procalcitonin, or interleukin 6 (IL-6), all of which are elevated in sepsis. Thus, the second consensus conference in 2001 modified these definitions. The criteria for sepsis were revised to include infection and a list of clinical and laboratory parameters to define sepsis. These criteria were based on an expansion of the clinical (eg, fever, tachycardia, and tachypnea) and laboratory parameters (eg, elevated or low white blood cell count and elevated C-reactive protein). The conference participants acknowledged that no single parameter or set of clinical or laboratory parameters was adequately sensitive or specific to diagnose sepsis. The severe sepsis criteria remained unchanged. Although several criteria are used to define organ dysfunction during sepsis, use of the Sequential Organ Failure Assessment (SOFA) score by Vincent and colleagues was recommended for this purpose. A more explicit definition for septic shock was also proposed: hypotension with a systolic blood pressure less than 90 mm Hg or a mean arterial blood pressure (MAP) less than 70 mm Hg, despite adequate fluid resuscitation.

The third consensus conference in 2015 redefined sepsis to simplify the terms and definitions based on analyses conducted using several large databases. This committee recommended abandoning the term *severe sepsis* and using *sepsis* to describe infection-induced organ dysfunction or tissue hypoperfusion. The document also recommended de-emphasizing the SIRS criteria. What was previously called *sepsis* (infection plus systemic manifestations of infection) would now simply be called *infection* with no differentiation from infection without systemic manifestation of infection. Organ dysfunction was defined as an increase in the SOFA score of 2 points or more. Septic shock was defined as vasopressor requirement to maintain a MAP of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia after intravascular volume repletion.

Despite these attempts to define sepsis and septic shock, early recognition remains a challenge because no specific test is available to diagnose sepsis. Tissue hypoperfusion can occur in the absence of hypotension and could be present for hours before organ dysfunction manifests. Since the 2001 definitions are currently used for both *International Classification of Diseases, Tenth Revision (ICD-10)* codes and the Centers for Medicare and Medicare Services

quality metrics, any major shift to the new definitions is likely to be slow and will require much planning and coordination.

EPIDEMIOLOGICAL CHARACTERISTICS

Incidence and Mortality

The incidence of sepsis in the United States is estimated to be 300 cases per 100,000 population. Approximately half of these cases occur outside of the ICU. One-fourth of patients who develop sepsis die during their hospital stay. The cumulative burden of organ failure is the strongest predictor of death, in terms of both the number of organs failing and the degree of organ dysfunction. Septic shock is associated with higher mortality compared with sepsis alone.

Several studies have found an increase in sepsis incidence and a decrease in sepsis-related deaths over the past 2 decades. National estimates of the epidemiological patterns of sepsis are based on the use of administrative data. The increase in the number of patients hospitalized with sepsis may be due to the aging population, increasing burden of chronic health conditions, and increased use of immunosuppressive therapy, transplantation, chemotherapy, and invasive procedures. Changes in coding practices, particularly the increased coding of organ dysfunction, may overestimate the rate of increase in the incidence of sepsis.

Although the mortality attributed to sepsis has increased over the past 2 decades, the case-fatality has declined. This may be due to nonspecific advances in medical care for the critically ill. The reduction in case fatality rate also may be due to changes in coding practices; less sick patients are now coded as *sepsis*. Furthermore, the length of stay has declined as patients are increasingly discharged to long-term acute care facilities before the recovery is complete, which leads to underestimation of the case-fatality rate during the sepsis hospitalization.

Cause and Site of Infection

Gram-positive infections are currently the most common cause of sepsis, and the incidence of multidrug-resistant gram-negative organisms is increasing. Critically ill patients are increasingly stricken with resistant strains of bacteria, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and extended-spectrum β-lactamases. While the incidence of fungal

sepsis continues to increase, the overall incidence is low compared with bacterial infection.

Respiratory tract infections, particularly pneumonia, are the most common type of infection. Other types of infection include genitourinary, abdominal, skin, and soft tissue infections; device-related infection; central nervous system infection; and endocarditis.

Risk Factors

Increased age, male gender, African American race, and chronic health conditions are important risk factors for sepsis. The incidence of sepsis increases disproportionately in older adults, and more than half of sepsis cases occur in patients older than 65 years. More than half of the patients who develop sepsis also have at least one chronic health condition. Sepsis is more likely to occur in individuals with chronic obstructive pulmonary disease, cancer, chronic kidney and liver disease, and diabetes mellitus. Other risk factors include residence in a long-term care facility, malnutrition, and the use of immunosuppressive medications and prosthetic devices. Finally, abnormalities in the immune response to infection, as described later, increase the risk of infection and sepsis. These abnormalities can be secondary to chronic diseases or age (immunosenescence).

Risk factors that increase susceptibility to sepsis also increase mortality following sepsis. The most important in-hospital risk factors associated with high mortality are the severity of illness and the number of organs failing.

Despite improved understanding of clinical risk factors influencing susceptibility to and outcomes of sepsis, it remains unclear why some subjects develop sepsis and succumb to the infection whereas others do not. Thus, genetic factors have been examined to explain variability in susceptibility and outcomes of infection. A study by Sorensen and colleagues suggested that genetic factors may be more important to the outcomes of infectious diseases compared with cardiovascular disease. In this study, children whose parents died from infectious causes had 5.8-fold increased risk of dying because of infections. In comparison, the increased risk of death due to cardiovascular causes was 4.5-fold if the children’s parents died of cardiovascular causes. Because sepsis is common and often fatal, the pattern of inheritance is unlikely to be Mendelian, where phenotypical differences are attributed to a single gene. Multiple genes may interact with pathogens (environmental factors) and influence susceptibility for and outcome

of sepsis. Some of the candidate genes that have shown promising results include tumor necrosis factor (TNF), plasminogen activator inhibitor 1, Toll-like receptors 1 and 4 (TLR-1 and TLR-4), and the Mal functional variant required for downstream signaling of TLR-2 and TLR-4.

The relative contribution of clinical and genetic factors to a patient's susceptibility for and outcome from sepsis is poorly understood. Genetic factors may play an important role in younger individuals but could be less important in older adults, for whom chronic diseases may play a more important role.

PATHOPHYSIOLOGICAL CHARACTERISTICS

The innate immune system plays a vital role in resistance to infectious disease, forming the first line of defense in the recognition and destruction of pathogens and allowing time for the acquired immune response to take effect. The innate immune system consists of physical and chemical barriers and humoral and cellular mediators. Components of the innate immune response are characterized by their rapid action, their lack of immunological memory, and their function as antigen-presenting cells that activate the adaptive immune system. The principal cellular components of the innate immune system include neutrophils, monocytes and macrophages, natural killer cells, and dendritic cells. These cells are able to recognize pathogens through the interaction of pathogen-associated molecular patterns (PAMPs) and TLRs. PAMPs include endotoxins or lipopolysaccharides (LPS) in gram-negative bacteria and lipoteichoic acid or peptidoglycan in gram-positive bacteria.

TLRs play a critical role in recognizing PAMPs and instructing the adaptive immune system to respond to infection. For instance, LPS binds to LPS-binding protein (LBP), a circulating mediator, and to cluster of differentiation (CD), located on the membrane of immune cells. This complex of LPS-LBP and CD14 signals through TLR-4 and eventually leads to nuclear translocation of nuclear factor-kB and activation of cytokines. More than 10 TLRs have been discovered with unique ligands, such as TLR-4, which is an LPS receptor, and TLR-2, which recognizes gram-positive cell walls.

The host-microbe interaction described above leads to the activation of several mediators within the innate immune system, including proinflammatory and anti-inflammatory cytokines and the coagulation cascade. The pathophysiological process of sepsis is complex and involves the interaction of different pathways. Key mechanisms are described below.

Uncontrolled Inflammation

Although activation of the innate immune response is necessary to eradicate infection, this response can be overwhelming and can lead to sepsis and death. The terms *uncontrolled*, *maladaptive*, and *dysregulated* are often used to describe inflammation in sepsis. This model of uncontrolled inflammation was based on animal models of sepsis, where high circulating concentrations of proinflammatory mediators, such as TNF, IL-1, and IL-6, were observed. However, several randomized clinical trials in humans where monoclonal antibodies were used to block endotoxin, proinflammatory cytokines, or their receptors have failed to improve survival or have worsened it. These results have challenged the theory that uncontrolled inflammation is a singular primary component of morbidity and mortality in severe sepsis.

Immune Suppression

Many patients with sepsis have a prolonged ICU course and often die following nosocomial infections. Experimental findings suggest a shift from helper T cell 1 (T_H1) response, where immune cells secrete proinflammatory cytokines, to T_H2 response, where anti-inflammatory cytokines, such as IL-4 and IL-10, predominate during the latter periods of sepsis. Another important finding is that septic patients have reduced expression of T_H1 cytokines, particularly TNF and interferon g, by monocytes in response to infectious stimuli in ex vivo studies. These changes in cell expression could represent a protective response against uncontrolled inflammation. Yet these changes may delay resolution of organ dysfunction and place individuals at higher risk of dying from hospital-acquired infections. Several terms have been proposed to describe these changes in immune cell function during infection and sepsis, such as *endotoxin tolerance*, *anergy*, *immunodepression*, and *cellular reprogramming*.

More than 100 immunomodulatory therapies designed to dampen the inflammatory response have failed. The causes for failure of these trials are multifactorial, but the lack of personalized strategies may be an important reason. Immunosuppression and inflammation are differentially expressed across patients and are difficult to distinguish clinically. Sepsis-induced immunosuppression is also a heterogeneous condition and may occur due to different pathways and mechanisms. Thus, many studies may have failed because therapies targeted the wrong pathways or were not personalized and were tested in inappropriate patients.

Other Mechanisms

During sepsis, coagulation proteins are activated, and anticoagulation (protein C system and tissue factor pathway inhibitor) and fibrinolysis (plasminogen activator inhibitor 1) pathways are impaired. Inflammatory mediators, such as TNF, initiate coagulation through the induction of tissue factor expression, primarily on monocytes and macrophages and on endothelial cells. The end result is activation of the coagulation cascade, which leads to microvascular thrombus formation, organ dysfunction, and bleeding.

Despite improved understanding of the involvement of the coagulation pathway, no therapies targeting the coagulation pathway are currently approved for sepsis. Drotrecogin alfa improved survival in patients with sepsis in a phase 3 trial and received Food and Drug Administration (FDA) approval. However, subsequent studies failed to demonstrate improvement in mortality, and the drug was withdrawn from the market. Other therapies, such as tissue factor pathway inhibitor and antithrombin III, were tested in clinical trials and had no impact on mortality.

Epithelial and Endothelial Dysfunction

Epithelial cell line organs, including the liver, kidney, lung, and intestine, are involved in multiple organ dysfunction syndrome. Thus, increased permeability and loss of the epithelial cell barrier are hypothesized to play an important role in this syndrome. For example, increased permeability of lung epithelial cells manifests clinically as acute lung injury or acute respiratory distress syndrome.

Similar to the epithelial system, the endothelium system plays an important role in sepsis. The endothelium possesses anticoagulant and antithrombotic properties, and damage to the endothelium activates the coagulation cascade and increases nitric oxide, which may mediate peripheral vasodilatation, hypotension, tissue hypoperfusion, and increased permeability, all of which are frequently observed during sepsis.

Persistent Inflammation-Immunosuppression Catabolism Syndrome

Recent publications describe a condition called *chronic critical illness* that includes patients with complex ICU courses who later experience recurrent organ dysfunction, including cognitive decline, recurrent infections, weakness with prolonged institutionalization, and malnutrition. Long-term survival is poor. Although the systemic inflammatory and procoagulant response may be

responsible for early primary cardiovascular and pulmonary deaths, poor outcomes in this patient population are thought to be due to persistent immune suppression, dysfunctional immunity, low-grade inflammation, and protein catabolism. The aggregate of these components in septic patients has been coined *persistent inflammation-immunosuppression catabolism syndrome*. This syndrome should not be confused with the post-ICU syndrome, which entails detrimental effects that persist in survivors of ICU hospitalizations regardless of the origin of their illness. Accompanying the low-grade inflammation and immunosuppression are ongoing loss of muscle mass, poor wound healing, lymphopenia, and predisposition to viral infections.

CLINICAL DIAGNOSIS

To ensure rapid implementation of effective therapies, the prompt diagnosis of sepsis is critical. The initial presumptive diagnosis of sepsis can be made in the presence of an infection and organ dysfunction criteria. The diagnosis of infection does not require microbiological or radiographic evidence. Only a clinical suspicion of infection and the presence of organ dysfunction is necessary. In these patients, the absence of hypotension but an elevated lactate level is often an indication of tissue hypoperfusion and should prompt early aggressive therapy. This clinical approach allows initiation of diagnostic steps, to identify a source of infection, and therapeutic steps, including early goal-directed therapy and antibiotics.

TREATMENT

The Surviving Sepsis Campaign guidelines for the diagnosis and management of sepsis were last published in 2012. These guidelines are an excellent source for review.

Antimicrobial Therapy and Source Control

Treatment for sepsis and septic shock rests on the triad of antimicrobial management, hemodynamic resuscitation, and source control. Selective and well-chosen antibiotics must be used in a timely fashion, dosed appropriately based on pharmacodynamic principles, and discontinued as early as possible to avoid the emergence of resistant microorganisms.

Observational studies have shown an association between delays in appropriate antibiotic treatment and higher risk of death. For example, a Medicare database

study of 14,000 elderly patients hospitalized with community-acquired pneumonia showed an increased risk of death when appropriate antibiotics were delayed 8 hours or more after hospitalization. A similar observation was made for patients who developed ventilator-associated pneumonia, with a delay in antibiotics increasing the risk of death by 7.7 times. Effective antimicrobial administration within the first hour of documented hypotension in sepsis is associated with increased survival, and mortality increases with each hour delay in effective antimicrobial therapy.

Antimicrobial therapy can be effective only in the context of appropriate source control. The need for such source control may be overlooked initially in many infections commonly found in the ICU, such as pneumonia-associated bacterial empyema, abscess, and *Clostridium difficile* colitis. Source control can include removal of implanted or tunneled devices, open surgical or percutaneous drainage of infected fluids or abscesses, and surgical resection of infected tissues. Efforts to identify infections requiring invasive forms of source control frequently require rapid radiographic imaging or immediate surgical intervention without imaging. Surgical source control typically follows aggressive resuscitative efforts to minimize intraoperative morbidity and mortality. In cases that involve rapidly progressive infections, as seen in necrotizing soft tissue infections, optimal management may require simultaneous aggressive resuscitation and surgical intervention. Earlier surgical intervention has been shown to have a significant impact on outcome in certain rapidly progressive infections, such as necrotizing fasciitis. The effectiveness of source control interventions should be reassessed at periodic intervals.

In approximately 20% to 30% of cases, the initial choice of antibiotics is incorrect, based on subsequent culture and sensitivity specimen results, which underscores the importance of optimal initial antimicrobial therapy. The risk of inappropriate antibiotic selection is increased when resistant microorganisms are not suspected or patients have received prior antibiotics. Should one empirically "choose poorly," mortality increases by 50% to 100%, as shown in septic shock and nosocomial pneumonia. Initial broad antibiotic coverage followed by de-escalation to narrow antimicrobial coverage following the results of cultures will maximize appropriate antibiotic coverage of inciting pathogens in septic shock and minimize selection pressure toward resistant organisms.

Microorganism eradication is directly related to optimizing the antimicrobial dosing regimen based on pharmacodynamic principles. Several studies have demonstrated that suboptimal dosing of antibiotics is common in ICU patients

with sepsis or septic shock because these conditions can substantially increase volumes of distribution and decrease clearance rates. Data are most well developed in reference to aminoglycosides but also exist for fluoroquinolones, lactams, and carbapenems. Failure to achieve targets on initial dosing has been associated with clinical failure. Early optimization of antimicrobial pharmacokinetics can improve outcome of patients with severe infection, including septic shock. In general, this is most easily achieved by initiating antibiotic therapy with high-end dosing regimens, and integrating pharmacy-driven protocols to maximize antimicrobial therapy.

Carefully selecting antibiotics, choosing an appropriate dose, writing orders, mixing bags in the pharmacy, transporting drug to the patient's bedside, obtaining vascular access for IV infusion, and having a nurse administer the agent are all steps that represent a complex process of care. Physicians tend to overlook the nuances in this process of care, and delays can occur at any point in the process. Last, although there is intense interest in novel biomarkers and molecular diagnostics of sepsis (eg, procalcitonin), convincing outcomes data are not available to warrant widespread use.

Hemodynamic Resuscitation

The purpose of aggressive, sustained hemodynamic support is to normalize both organ perfusion and arterial pressure and restore the balance between oxygen delivery and consumption. Preserving a sufficient MAP is fundamental to ensuring adequate organ perfusion and function. The MAP is a better reflection of the arterial pressure, and 60 to 70 mm Hg has traditionally served as a goal for resuscitation in North America. One study comparing MAPs of 65, 75, and 85 mm Hg found no difference in organ perfusion indices. A recent multicenter trial compared MAPs of 65-70 mm Hg and 80-85 mm Hg in 776 septic shock patients receiving high-dose vasopressors and found no difference in 28-day mortality. Interestingly, patients in the higher MAP arm had more new atrial fibrillation, and those in the chronic hypertension subgroup had less renal replacement therapy.

Fluids

We are entering a time of considerable uncertainty as to choice of crystalloid fluids for resuscitation and the titration of fluids versus vasopressors to maintain MAP. Traditionally, vasopressors have been minimized through persistent aggressive fluid resuscitation. In 2004, crystalloids and colloids of all nature

were recommended equally for fluid resuscitation of septic shock. According to current recommendations, crystalloids are the fluid of choice for initial resuscitation; in patients who require large amounts of fluid to stabilize intravascular volume, hetastarch colloids should be avoided and albumin is preferred. The association of poor outcome with high input-output ratios has raised concern about the potential detriment of overly aggressive fluid administration in resuscitation of septic shock. However, patients with more severe sepsis would be expected to have more severe venodilatation and more severe capillary leak and by definition require more fluids to maintain MAP. Regardless of the reason for poor outcomes following fluid resuscitation, it is likely that both underresuscitation and overresuscitation occur. For each patient there is likely an optimal mix of fluid and vasopressor to maintain MAP, and the challenge for the clinician is to determine this optimal mix. Even if early aggressive fluid resuscitation saves lives, there is likely a price to pay downstream with the fluid that is left in the extravascular tissues once the pathogens are eradicated and the inflammation response is quenched. This fluid is typically mobilized in patients with adequate renal function as capillary membranes heal. Whether this diuresis could be encouraged with intravenous diuretic after a patient's infection is cleared and tissue hypoperfusion no longer exists is a matter that requires more research.

In a single-institution clinical trial of 263 patients with sepsis or septic shock, Rivers and colleagues examined the hypothesis that early, protocolized, goal-directed resuscitation improves survival. This study examined goal-directed resuscitation and determined it to be an effective approach when initiated within the first 6 hours in the emergency department and well prior to ICU admission, as opposed to the previous studies that targeted later ICU care. A delay in fluid resuscitation may prevent reversal of tissue injury from occult ischemia. The intervention arm also entailed protocolized care whereby fluid boluses were given based on central venous pressure to optimize preload, vasopressor therapy was started to improve MAP (>65 mm Hg), and packed red blood cells were transfused and dobutamine infusions used to improve oxygen delivery if mixed venous oxygen saturation remained less than 70%. The control group received conventional monitoring, with mostly back-loaded resuscitation in the ICU. Patients randomized to the protocolized, goal-directed approach had a significant decrease in mortality and morbidity (30.5% in the early goal-directed therapy group vs 46.5% in the control group, $P = 0.009$).

Since the 2001 publication of the Rivers trial, 3 recently completed multicenter

trials of early goal-directed therapy of early septic shock failed to find a mortality benefit. Why the difference? First, the 3 trials did not test whether early recognition or care was better than late recognition or care. In all trial patients, including those in the control arm, septic shock was promptly recognized; antibiotics and fluids were provided, and MAP was quickly restored. Thus, the trials support the primacy of early diagnosis and treatment. Second, sepsis care awareness and mortality have changed significantly since the late 1990s. From 2000 to 2012, sepsis mortality in Australia decreased from 35% to 18.5%. Thus, in 2016, all agree that therapy should be provided early and should be directed toward goals; the only debate is which physiological goals. Focused ultrasonography and arterial pulse contour analysis hold promise to help define endpoints for fluid resuscitation in shock.

Vasopressors should be started for hypotension refractory to initial fluid resuscitation and for profound, near-arrest hypotension while fluids are simultaneously delivered. The choice of vasopressor is based on its efficacy to improve hemodynamics and its adverse effect profile. Norepinephrine is the vasopressor of choice for septic shock and has been shown to be superior to dopamine. Norepinephrine is expected to have more powerful vasopressor effect than dopamine and, like dopamine, is expected to raise both MAP and cardiac output. Although early studies suggested that low-dose dopamine can prevent renal dysfunction, a subsequent randomized controlled trial did not confirm these findings.

Choosing a vasopressor will by necessity remain somewhat of an art. For example, despite a general preference for norepinephrine, if a patient with septic shock has relative bradycardia and known low cardiac output despite adequate volume resuscitation, then dopamine is likely the better choice. Although a second pressor is often added to norepinephrine when doses of 30 to 40 mg/min fail to achieve MAP target, considerably higher doses of norepinephrine are chosen by some (40-80μg/min). No evidence is available to guide any limitation of norepinephrine dosing. When MAP remains low despite fluid resuscitation and norepinephrine, either low-dose vasopressin (up to 0.04 U/min) or epinephrine is recommended as additive therapy. A prospective randomized trial compared mortality in 330 subjects with septic shock who received 1 of 2 regimens: norepinephrine and dobutamine vs epinephrine. The trial, designed to assess large differences in mortality, showed no difference in outcomes between the 2 regimens. Lactic acidosis was more common in the subjects who received epinephrine.

Phenylephrine, a pure vasoconstrictor, is generally avoided unless cardiac output is known to be high or other vasopressors have produced arrhythmias. Phenylephrine is a relatively pure α-adrenergic agonist, has minimal or absent inotropic effects, and tends to cause reflex bradycardia. For that reason, it can be useful in the context of excessive tachycardia or concurrent tachyarrhythmias.

Vasopressin acts on vascular smooth muscle, independent of adrenergic receptors, by binding to V1 receptors. The availability of a nonadrenergic vasopressor is attractive, because septic shock is typified by downregulation of adrenergic responsiveness. Moreover, the posterior pituitary gland becomes rapidly depleted of native vasopressin with prolonged shock, leading to a hormonal deficiency. However, the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock (VASST) trial, a multicenter, randomized, double-blind study to compare vasopressin (0.01-0.03 U/min) and norepinephrine (5-15 μg/kg/min) in patients with septic shock, showed no difference in 28-day mortality. This trial did demonstrate that doses of vasopressin up to 0.03 U/min are safe. In addition, selepressin is being tested in a multicenter randomized controlled trial in patients with septic shock.

Immune Modulation

Corticosteroids

The use of corticosteroids to treat septic shock remains controversial. Although early clinical trials and animal studies initially supported the use of high doses of corticosteroids for a short duration, they ultimately were associated with worse outcomes in randomized clinical trials.

Several studies have demonstrated that administration of low-dose or stress-dose steroids (200-300 mg of hydrocortisone daily equivalent) to patients with septic shock can decrease vasopressor requirements and lead to earlier resolution of septic shock. In a prospective, randomized multicenter trial of 299 French men and women in septic shock by Annane and colleagues, patients underwent an adrenocorticotropic hormone (ACTH) stimulation test and then received hydrocortisone (50-mg IV bolus 4 times daily) and fludrocortisone (50-mg oral dose once daily) for 7 days. Remarkably, approximately 70% of the patients were found to be adrenally insufficient. Corticosteroid therapy decreased 28-day mortality by 10% in ACTH nonresponders. Corticosteroid administration provided no benefit in patients who successfully responded to the ACTH challenge.

The Corticosteroid Therapy for Septic Shock (CORTICUS) trial by Sprung et al was a randomized multicenter study and examined the role of low-dose hydrocortisone in septic shock. In contrast to the results of the trial by Annane and colleagues, the CORTICUS trial showed no significant difference in 28-day mortality among patients who did and did not receive hydrocortisone (34.3% in the hydrocortisone group and 31.5% in the placebo group, $P = 0.51$). Furthermore, no difference in survival was found in subgroups who were responders or nonresponders according to results of the ACTH stimulation test. The proportion of patients in whom shock was reversed was similar among those who did and did not receive hydrocortisone, but shock reversal was faster in the group who received hydrocortisone.

The conflicting results of these trials may have occurred for several reasons. First, patients enrolled in the Annane trial were sicker than those enrolled in the CORTICUS trial. In the Annane trial, entry criteria included persistent hypotension despite fluid resuscitation and vasopressors (blood pressure unresponsive to vasopressors), whereas in the CORTICUS trial, the entry criterion was vasopressor requirement following fluid resuscitation (most patients had blood pressures that were responsive to vasopressors). Second, patients were enrolled in the Annane trial within 3 hours of the onset of shock, whereas in the CORTICUS trial, patients could be enrolled up to 72 hours after the onset of shock. Therefore, low-dose hydrocortisone is most likely to benefit patients with shock that is not responsive to vasopressors. Furthermore, no evidence is available to support use of hydrocortisone to treat sepsis in the absence of shock. To address these conflicting results, a large ($N = 3{,}800$), multicenter randomized clinical trial is underway to determine the efficacy of low-dose hydrocortisone in patients with septic shock.

An additional explanation for conflicting findings is the significant variability found in the results of cortisol assays among research centers and also between a given research center and the reference laboratory source. Finally, it is possible that the circulating free cortisol level is the primary determinant of a response to steroids. The data published to date have examined circulating total cortisol levels. Free and total cortisol levels may vary significantly based on serum protein concentration. These observations and the results of the CORTICUS study suggest that results of ACTH stimulation tests should not guide the decision to administer low-dose hydrocortisone in septic shock. The Surviving Sepsis Campaign guidelines recommend that low-dose hydrocortisone (200 mg/d) be considered in patients who have hypotension despite fluid resuscitation

and are poorly responsive to vasopressors.

Other Support Modalities

Supportive therapies are key to management of patients with sepsis. These include management of mechanical ventilation, sedation and neuromuscular blockage, glucose control, and renal replacement therapy. Many of these issues are covered in other chapters, and some of them are covered briefly below.

Glucose Control

Hyperglycemia and insulin resistance are common in sepsis. In 2001, Van den Berghe and colleagues demonstrated that intensive insulin infusions titrated to strict glycemic control (80-110 mg/dL) in critically ill surgical patients could be beneficial. The patients randomized to intensive insulin therapy experienced a mortality reduction of 50%, with fewer septic episodes, fewer instances of bacteremia, fewer cases of multiple organ failure, fewer instances of critical illness polyneuropathy, less time on artificial support such as mechanical ventilation and hemodialysis, and fewer transfusions.

A second study by Van den Berghe targeted medical ICU patients and used the same strict upper threshold target of 80 to 110 mg/dL. In the intention-to-treat analysis, no significant difference was found in mortality (40% in the conventional treatment group vs 37.3% in the intensive treatment group, P = 0.33). Morbidity was lower in the intensive insulin therapy group, as evidenced by lower incidence of acute kidney injury and earlier weaning from mechanical ventilation. The investigators also reported hypoglycemia in 5.2% of the intensive insulin group compared with 0.8% of the control group.

A multicenter randomized trial in Germany examined the role of intensive insulin therapy using a similar insulin protocol. The trial was stopped early (N = 537) because of a high incidence of hypoglycemia, defined as blood glucose 40 mg/dL or less (17.0% vs 4.1%, P = 0.001). No difference was observed in 28-day mortality.

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) was a multicenter, multinational randomized clinical trial involving 6,100 subjects from 42 hospitals in Australia, New Zealand, Canada, and the United States. The NICE-SUGAR investigators compared conventional therapy (maintaining the glucose concentration at ≤180 mg/dL) to a regimen of intensive glucose control with a target glucose of 81 to

108 mg/dL. The primary outcome, 90-day mortality, was higher in the intensive glucose control group (27.5% vs 24.9%, $P = 0.02$). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratios for death in the intensive control group, 1.31 and 1.07, respectively; $P = 0.10$). Severe hypoglycemia (blood glucose level ≤40 mg/dL) was reported in 206 of 3,016 patients (6.8%) in the intensive control group and 15 of 3,014 patients (0.5%) in the conventional control group ($P < 0.001$). The higher mortality in the intensive glucose control group occurred despite a much lower rate of hypoglycemia than reported in any previous studies of combined surgical and medical patients. Note that the findings of NICE-SUGAR do not justify neglecting glycemic control. Rather, a glucose level higher than 180 mg/dL should be treated to achieve a target blood glucose concentration between 120 and 180 mg/dL.

LONG-TERM OUTCOMES

The traditional focus of care in patients with infectious disease has been to reduce short-term mortality, and clinical trials have used 28-day or 90-day mortality as an end point. However, recent studies suggest that infection may worsen long-term outcomes. Although it is commonly believed that serious infection occurs in older subjects with chronic health conditions and that these conditions contribute to higher mortality even after recovery from acute illness, several studies show that the higher long-term mortality is independent of poor baseline functional and health status. These studies suggest that pathophysiological processes initiated during infection may lead to higher long-term mortality. For instance, recent studies suggest that the immune response activated during an acute infection can remain upregulated during recovery and is associated with higher long-term mortality, particularly that due to cardiovascular disease.

Adverse long-term outcomes are not limited to increased mortality risk. Several observational studies have shown that patients with sepsis and critical illness have higher risk of long-term cognitive impairment and impaired functional status. These sequelae impair the quality of life and increase the risk of admission to rehabilitation facilities and nursing homes after hospital discharge. Sepsis survivors also are at high risk for rehospitalization within the initial 90 days after hospital discharge. Common reasons for readmissions include respiratory disease, repeat episodes of infection, and cardiovascular diseases such as heart failure, arrhythmias, and acute coronary syndromes.

Finally, acute infections may worsen chronic diseases, and the relationship between acute infection and chronic illness is bidirectional. Whereas the increased burden of chronic health conditions increases the risk of infection and sepsis, survivors of infection may develop a higher burden of chronic disease. For example, individuals with kidney disease are at higher risk for serious infection; an episode of serious infection can lead to acute kidney injury and eventually chronic dialysis. Similarly, it has been shown that infection with influenza is associated with increased risk of cardiovascular disease. These examples underscore the complex relationship between infection and underlying chronic disease, where a chronic disease both serves as a risk factor for infection and is modified by the infectious event. The worsening of chronic disease following infection is in turn a risk factor for subsequent acute illness, thereby initiating a spiral of events that can ultimately lead to death.

SUMMARY

Morbidity and mortality from sepsis and septic shock remain high. Early identification of patients with sepsis, in particular sepsis-induced tissue hypoperfusion, is a high priority. The optimal management of patients with sepsis includes prompt hemodynamic resuscitation, swift initiation of appropriate antimicrobial therapy, source control, and other supportive modalities. The role of immune modulation remains unclear. Providing performance feedback to healthcare practitioners as part of a quality assurance program is important for effective treatment of sepsis.

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CHAPTER 10

Hypovolemic and Hemorrhagic Shock

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Key words: shock, fluids, damage control resuscitation

Shock is the final common pathway for multiple disease states and is classified into 4 common types: hypovolemic-hemorrhagic, cardiogenic, obstructive, and distributive. These divisions are not exclusive of one another. This chapter provides a framework for understanding the complex entities of hypovolemic and hemorrhagic shock. The evaluation and management of hemorrhagic shock are more complicated than required for simple hypovolemia and merit special emphasis.

DEFINITIONS, CAUSES, AND PATHOPHYSIOLOGICAL CHARACTERISTICS

Shock is marked by inadequate oxygen delivery to the tissues or abnormal oxygen utilization by the tissues that results in an inability to meet metabolic demand, ultimately causing cellular injury. The disease state encompasses the initial hypoperfusion as well as the organ dysfunction and systemic disease that follow. On a cellular level, hypoxic conditions lead to mitochondrial dysfunction, alterations in the cell membrane, release of oxygen free radicals, cytokine production, and subsequent activation of multiple inflammatory cascades.

Hypovolemic shock can be defined as decreased circulating blood volume that causes inadequate oxygen delivery. Hypovolemic shock can be differentiated from other forms of shock by low filling pressures and high systemic vascular resistance. Low intravascular volume leads to decreased venous return and low stroke volume, which, if severe enough, can lead to decreases in cardiac output and blood pressure. However, the body fights to maintain cardiac output and

therefore maintain tissue perfusion with several compensatory mechanisms:

- Activation of the sympathetic nervous system leads to the release of catecholamines and subsequent tachycardia, tachypnea, increased glycogenolysis, and vasoconstriction. Blood flow is shunted away from the skin, muscles, and gut to preferentially perfuse vital organs such as the heart and brain.
- Activation of the renin-angiotensin-aldosterone system (RAAS) causes vasopressin-induced vasoconstriction and sodium retention. Sodium retention results in fluid shifts from the extravascular to the intravascular compartment.
- Tissue oxygen extraction increases to help meet metabolic demand. Normally, tissue oxygen extraction is around 25%, and it can increase to a maximum of approximately 50%.

Compensated shock occurs when increased oxygen extraction and activation of the sympathetic nervous system and RAAS are enough to meet tissue oxygen demands. However, the capacity of these mechanisms to compensate for intravascular volume loss is not limitless. Decompensated shock occurs when these mechanisms are unable to keep up with oxygen demands and anaerobic metabolism begins.

Hypovolemic shock can be divided into hemorrhagic and nonhemorrhagic causes. The American College of Surgeons has developed a classification system for hemorrhagic shock that provides a correlation between presentation and volume of blood loss (**Table 1**). Although this classification system is widely accepted, patient presentations vary and may not match these classifications precisely. Because of numerous compensatory mechanisms, patients in hemorrhagic shock typically will not become hypotensive until they are in class III shock, and the presence of hypotension (if due to hemorrhage alone) generally indicates that a profound degree of blood loss has already taken place.

Table 1. American College of Surgeons Classification of Hemorrhagic Shock

	Class I	**Class II**	**Class III**	**Class IV**
Blood loss, mL	<750	750-1,500	1,500-2,000	>2,000
Blood loss, %	<15	15-30	30-40	>40

Pulse, beats/min	<100	100-120	120-140	>140
Systolic blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	14-20	20-30	30-40	>35
Urine output, mL/h	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Adaptation of the original table from the 9th edition ATLS Student Manual. American College of Surgeons Committee on Trauma. *ATLS Advanced Trauma Life Support—Student Course Manual: Ninth Edition.* American College of Surgeons, 2012. Reproduced with permission from the American College of Surgeons.

Hypovolemic shock that is not caused by hemorrhage can be seen with poor fluid intake, increased fluid losses, or redistribution of fluid. The majority of causes of hypovolemic shock are outlined in **Table 2**.

Table 2. Causes of Hypovolemic Shock

Hemorrhagic
• Trauma
• Gastrointestinal bleed (upper or lower)
• Postsurgical bleed
• Bleeding or ruptured abdominal aortic aneurysm
• Retroperitoneal bleed
• Arteriovenous fistula or graft bleed
• Postpartum hemorrhage
• Ruptured ectopic or ovarian cyst
Nonhemorrhagic
• Decreased intake, dehydration
• Increased output

Vomiting
Diarrhea
Gastrointestinal fistula
Polyuria (ie, diabetes insipidus, diabetic ketoacidosis)
• Third spacing or insensible losses
Burns
Heat exhaustion, heat stroke
Post surgery
Pancreatitis

DIAGNOSIS AND ASSESSMENT

History and Physical Examination

A thorough history and physical examination are key for diagnosing and assessing the severity of hypovolemic and hemorrhagic shock. While many cases of hypovolemic shock are readily apparent, others are more subtle. Specific points to address include the following:

Hemorrhage

- Inherited coagulopathy
- Liver disease
- Malnutrition
- Use of anticoagulants (ie, antiplatelet agents, warfarin, novel oral anticoagulants)
- Traumatic bleeding: mechanism of injury, concomitant injuries, magnitude of force, trajectory (in penetrating trauma)
- Postsurgical or postprocedural bleeding: nature of surgery or procedure, potential sites for bleeding

- Nontraumatic, nonsurgical bleeding: comorbidities or recent events that could be associated with bleeding, such as peptic ulcer disease, atherosclerosis with abdominal aortic aneurysm, and pregnancy

Nonhemorrhagic Volume Loss

- Environmental conditions such as extreme heat
- History of gastrointestinal losses: vomiting, diarrhea, fistula, short-gut syndrome
- Burn injury: surface area and depth
- Baseline hydration status

As brain perfusion decreases, a patient may be anxious or have an altered mental status. Severe hypovolemic shock is associated with an altered level of consciousness. A patient usually will be tachypneic, tachycardic, and hypotensive. The skin will be pale, cool, and clammy. Urine output will progressively decline, and the appearance of the urine will usually become more concentrated as shock worsens. In the case of trauma, a full examination is needed to look for both obvious and occult injuries.

Unfortunately, although clinicians rely heavily on vital signs, they may not reflect the presence or severity of shock. Many bedside practitioners believe that hypotension is synonymous with shock, but there is no blood pressure cutoff that reliably indicates poor tissue perfusion. For example, a systolic blood pressure of 90 mm Hg may be relatively normal for either young, healthy patients or those with chronic liver insufficiency, but in a patient with chronic hypertension this value could represent a very severe decline in cardiac output and perfusion. Similarly, compensatory vasoconstriction might result in an apparently adequate blood pressure even in the setting of significant volume loss and end organ damage. For instance, a recent study of patients taken to the operating room (OR) with penetrating abdominal trauma and normal vital signs showed that whereas the majority of patients had minor (<750 mL) blood loss, more than 25% of the patients had class II, III, or IV hemorrhage despite normal vital signs.

Young patients have the ability to maintain vital signs even in the presence of significant blood loss. In contrast, elderly patients have significantly less reserve and may be hypotensive even with minimal blood loss. Many common medications can cloud the interpretation of vital signs. The classic example is a

patient receiving β-blockers who may not be able to mount the expected tachycardia in response to volume loss. Finally, other conditions often occur simultaneously with shock that can cause abnormal vital signs, such as pain or anxiety.

Laboratory Evaluation

Hypovolemic shock results in organ dysfunction. Thus, abnormal laboratory values can act as surrogates for inadequate perfusion on a cellular level. For example, hypovolemic shock can cause elevated creatinine due to decreased renal blood flow and possibly an elevated troponin level from demand myocardial ischemia (especially if the patient has underlying cardiac disease). However, neither acute kidney injury nor troponinemia is sensitive to or specific for shock.

Markers of Perfusion: Lactate and Base Deficit

Ideally, a laboratory marker for shock would be sensitive to poor overall perfusion and anaerobic metabolism. Since lactate is a byproduct of anaerobic metabolism, lactate is commonly used as a marker of shock. However, hyperlactatemia does not point to a specific type of shock (hypovolemic-hemorrhagic vs distributive, cardiogenic, or obstructive). Further, several other conditions can cause elevated blood lactate levels, including hepatic insufficiency, thiamine deficiency, and intracellular alkalosis.

Despite these possible confounders, studies have shown that the trends in lactate levels over time (more so than the initial level) correlate with outcome. As shock persists, lactate remains elevated. In a small study of trauma patients admitted to the ICU, patients with lactate levels that normalized to less than 2 mmol/L within 24 hours after initial injury had a mortality of less than 10%, whereas patients whose levels normalized more than 48 hours later had a mortality rate of 80% to 86%. While these results are provocative, no strong data are available to suggest using lactate as an isolated endpoint in resuscitation for hypovolemic-hemorrhagic shock.

The base deficit is the amount of base (in millimoles) needed to titrate 1 liter of whole blood to a pH of 7.40 and as a result reflects the extent of anaerobic metabolism and resulting acidosis. The value can be affected by resuscitation fluid or the administration of bicarbonate. Base deficit has been studied extensively in trauma given the ability of providers to obtain a rapid result from

an arterial blood gas analysis. The initial level has been found to correlate with transfusion requirements, organ dysfunction, morbidity, and mortality following trauma. The base deficit is also a better predictor of outcome than is pH alone. This is likely because of the compensatory mechanisms that strive to maintain a normal pH. Because increases in base deficit resulting from causes other than lactic acidosis (ie, normal saline resuscitation resulting in a hyperchloremic acidosis) do not correlate with increased mortality, subsequent measurements of base deficit may not accurately reflect the most current shock state.

Markers of Bleeding: Hemoglobin and Hematocrit

Hemoglobin and hematocrit levels are not reliable in early shock. When bleeding occurs, whole blood is lost, and consequently all components decrease by a similar ratio: The value of the hemoglobin or hematocrit at this point will not differ significantly from values prior to blood loss. A normal hemoglobin level therefore does not rule out active bleeding. An early decrease in hemoglobin is often due to fluid resuscitation alone. Additionally, activation of RAAS draws fluid into the intravascular space. Only after this has occurred will a decrease in hemoglobin be seen. Hemoglobin values drawn early after blood loss may help to identify patients with preexisting anemia who may be more sensitive to blood loss. The rate of change in hemoglobin over time may be more predictive of the severity of bleeding.

Markers of Coagulopathy

Coagulopathy is quite common in shock, especially in hemorrhagic shock. Coagulopathy can be dilutional, preexisting, or due to acute trauma. Understanding the coagulopathic state of a patient in hemorrhagic shock can be vital in guiding resuscitation. Standard markers of coagulopathy include prothrombin time and international normalized ratio (PT-INR), partial thromboplastin time (PTT), fibrinogen, and platelet count. Using these parameters to evaluate coagulopathy in acute shock states entails several drawbacks. Most important, laboratory tests of the PT-INR and PTT do not reflect in vivo conditions. Specifically, clotting in the laboratory does not depend on the complex cellular interactions necessary for activation of clotting cascade in vivo. Furthermore, blood samples are warmed to normal body temperature. Many patients with shock have significant hypothermia and as a result have a significant coagulopathy that will not be reflected in standard laboratory tests. In addition, testing of platelet and fibrinogen levels is quantitative and, as such, provides no assessment of function. Finally, these tests are time-consuming. Due

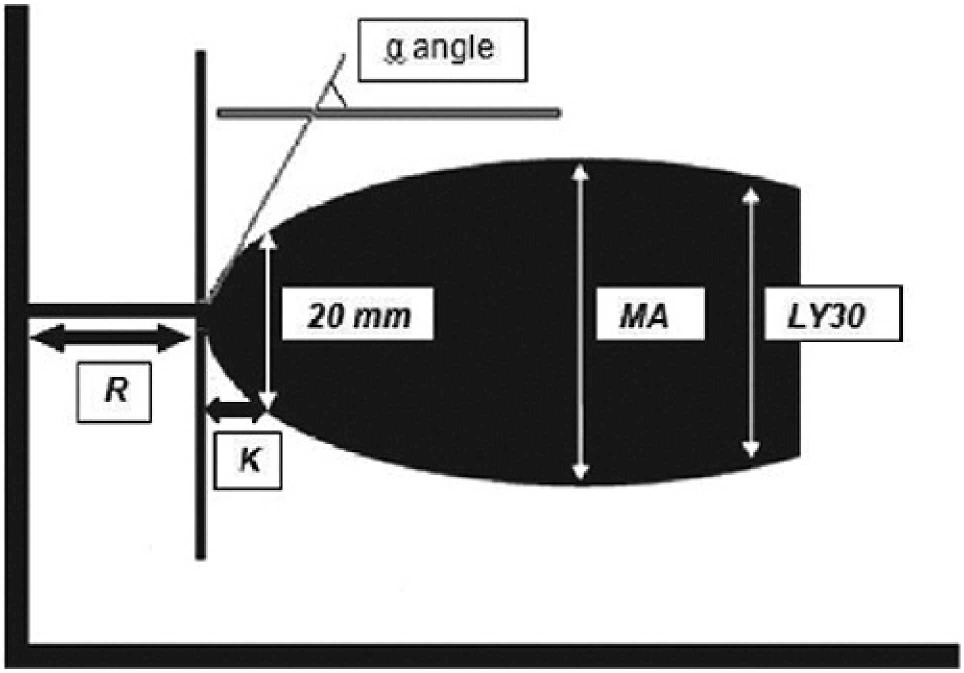
to the time required to obtain laboratory results, these results will not reflect the current condition of an actively bleeding patient and therefore may not be helpful in guiding resuscitation.

Viscoelastic hemostatic assays may be a more useful way to assess coagulopathy. These assays can be performed at the bedside and provide a functional evaluation of blood clotting. Thromboelastography® (TEG®, Hemoscope Corporation, Niles, IL) and Rotational Thromboelastometry® (ROTEM®; Tem International GmbH, Munich, Germany) are the two commercially available devices. Both tests provide similar information using different mechanics. **Figure 1** is an example of a normal TEG® tracing, and **Figure 2** provides examples of both normal and abnormal TEG® results. The tracing quantifies the kinetics of clot formation and lysis. The components of the TEG® include the following:

- R (reaction) time: The time to initial fibrin formation. This is prolonged by factor deficiency and heparin effect but reduced in hypercoagulable conditions.
- K (clot formation) time: The time from the R time until the clot has reached a particular level of firmness; a measure of clot kinetics.
- α angle: Angle formed by a line between R and K. The α angle is another measurement of clot kinetics. Both the K time and α angle are affected by factor levels, platelet number and function, and fibrin levels.
- MA (maximum amplitude): Greatest amplitude reached; represents maximum clot strength. This is affected most by platelet number and function and is affected by fibrinogen as well.
- LY30: Measures percentage of lysis 30 minutes after MA. This component reflects fibrinolysis.

Using the results from the TEG® tracing, the clinician can determine the exact nature of coagulopathy and thus potentially resuscitate the patient more appropriately.

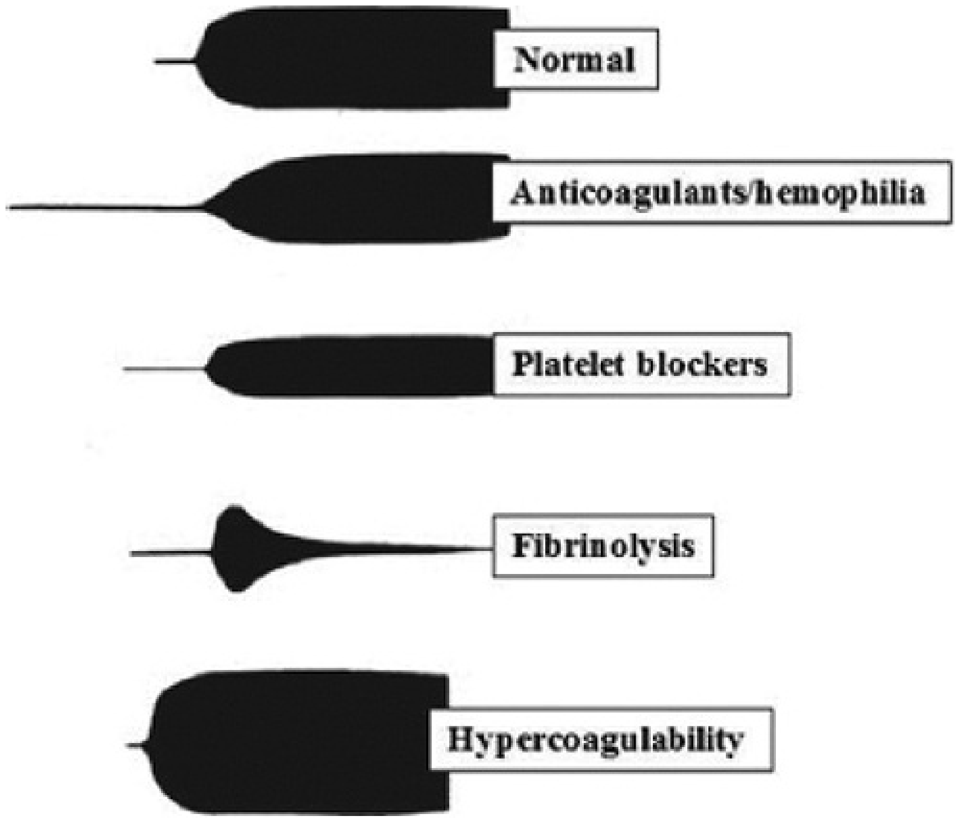
Figure 1. A representative signature waveform of a normal TEG tracing



R (seconds) is time of latency from start of test to initial fibrin formation. K (seconds) is time taken to achieve a certain level of clot strength (amplitude of 20 mm). α angle (degrees) measures the speed at which fibrin build-up and cross-linking take place, hence assessing the rate of clot formation. MA (millimeters) represents the ultimate strength of the fibrin clot. LY30 (%) is the percentage decrease in amplitude at 30 minutes post-MA and gives a measure of the degree of fibrinolysis.

da Luz LT, Nascimento B, Rozoli S. Thrombelastography (TEG): practical considerations on its clinical use in trauma resuscitation. *Scand J Trauma Resusc Emerg Med*. 2013;21:29.

Figure 2. Examples of normal and abnormal tracings on TEG



In the normal tracing, R, K, α angle, and MA are normal. In a patient receiving anticoagulants or with hemophilia, there is a deficit of coagulation factors; R and K are prolonged and the α angle and MA are decreased. In platelet dysfunction, R is normal, K is prolonged, and MA is decreased. In fibrinolysis, R is normal and MA continuously decreases. In hypercoagulability, R and K are decreased and the α angle and MA are increased.

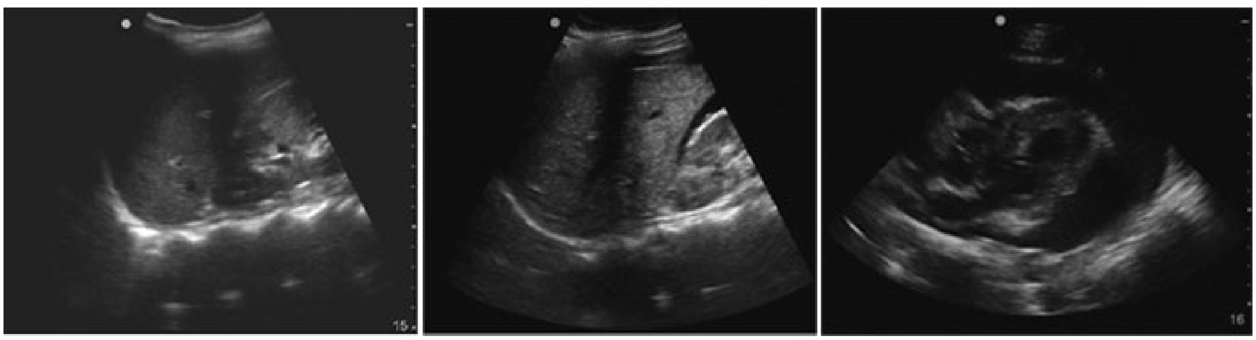
da Luz LT, Nascimento B, Rozoli S. Thrombelastography (TEG®): practical considerations on its clinical use in trauma resuscitation. *Scand J Trauma Resusc Emerg Med*. 2013; 21:29.

Several drawbacks of both these assays limit their widespread use. The physical machines require a significant financial investment, and staff must be specially trained to perform the tests. Quality control is also problematic. With TEG®, the analysis is made by the interactions of a small oscillating cup and a thin plastic pin suspended in the sample. With ROTEM®, the cup is stationary while the pin oscillates. Even a small perturbation alters results dramatically. Finally, definitive proof of the superiority of TEG® or ROTEM® over conventional evaluation of coagulopathy at the bedside is lacking. Studies show a reduction in bleeding and in the transfusion requirement with the use of TEG® or ROTEM®, but no mortality benefit.

Ultrasound Evaluation

The focused assessment with sonography in trauma (FAST) examination is often used to evaluate for bleeding in patients with suspected hemorrhagic shock. It can diagnose intra-abdominal bleeding and pericardial effusion or tamponade (**Figure 3**). The FAST examination cannot quantify the amount of blood present nor can it differentiate between blood and other fluid (eg, ascites). It also cannot diagnose retroperitoneal bleeding. Abdominal ultrasound can be useful in making other diagnoses resulting in hemorrhagic shock, such as ruptured aortic aneurysm or ruptured ectopic pregnancy.

Figure 3. Focused assessment with sonography for trauma (FAST) examination



A B C

(A) Normal view of Morrison's pouch (potential space between liver and kidney) in the right upper quadrant. (B) FAST positive with hypoechoic fluid seen in Morrison's pouch and on top of liver. (C) FAST positive subxiphoid view showing tamponade physiology with pericardial effusion impinging on right ventricle during diastole.

Images courtesy of Dr Sierra Beck, Emory University School of Medicine, Atlanta, Georgia.

Ultrasound is being used increasingly to assess volume status in patients with undifferentiated shock both in the emergency room and in the ICU. The majority of the studies evaluating the use of inferior vena cava (IVC) ultrasound and the rapid ultrasound in shock (RUSH) examination were conducted in patients with presumed septic or undifferentiated shock. The data supporting the use of IVC ultrasound in determining fluid status are more robust in mechanically ventilated patients. However, studies done in awake patients suggest that a small IVC (<2 cm diameter) with greater than 50% collapse upon inspiration also correlates with volume responsiveness. The RUSH examination consists of a basic evaluation of the heart (looking for pericardial effusion and global left ventricle and right ventricle function), IVC ultrasound, FAST examination, lung ultrasound (effusions, pneumothorax, A lines and B lines), and aortic ultrasound. In a small study evaluating the RUSH protocol in undifferentiated shock, the protocol had a sensitivity of 100% and specificity of 94.6% for hypovolemic shock.

Other markers of fluid responsiveness that often are used to determine which patients either have a component of hypovolemic shock or may respond to fluids include stroke volume variation, pulse pressure variation, passive leg raise, and empirical fluid loading. In general, active rather than static measurements are preferred.

MANAGEMENT

The overall goal in the management of shock is to correct the underlying cause, if possible, and maintain oxygen delivery to tissues. In patients with severe shock secondary to trauma, the lethal triad of coagulopathy, acidosis, and hypothermia becomes increasingly significant. Acidosis results from prolonged hypoperfusion and can exacerbate coagulopathy because coagulation factors can be dysfunctional in acidemia. Hypoperfusion causes hyperfibrinolysis, and coagulopathy is further worsened by the dilutional effect of intravenous fluids (IVFs) and red blood cell (RBC) transfusion. Patients in hemorrhagic shock are unable to maintain body temperature, which is further exacerbated by environmental factors (prolonged scene extrication, removal of clothing). Hypothermia also promotes coagulopathy and further bleeding. Worsening of any one of these variables leads to a worsening of all of them in a vicious cycle that leads to deterioration and ultimately death.

Airway and Breathing

Clinicians should use a low threshold to establish a secure airway and initiate mechanical ventilation in a patient in severe hemorrhagic shock. These procedures improve oxygen delivery. In addition, respiratory muscles require a disproportionate percentage of the cardiac output, especially in the case of the increased work of breathing that would be required to support declining oxygen delivery to tissues. Intubating a patient redistributes this blood flow. In addition, when the work of breathing is decreased, more oxygen is available for perfusion of other organs. A discussion of induction agents is beyond the scope of this chapter, but it is important to note that patients in shock require a significant dose reduction.

Vascular Access

Securing vascular access is one of the early priorities in the management of any patient with shock. Although many practitioners place a central venous catheter

in patients with hypovolemic or hemorrhagic shock, a standard triple-lumen central venous catheter is generally not appropriate for these patients. Flow rate is directly proportional to radius of the catheter and inversely proportional to catheter length. Thus, long catheters have significantly slower flow rates than short catheters. In the event that a large peripheral line (ie, 14- or 16-gauge IV) cannot be placed, it is essential to place either a large single lumen catheter such as a 9 French introducer, or a large catheter with at least one 12-gauge lumen. Many of the multilumen catheters will have much smaller radii.

Control Bleeding

Localize the Source

Resuscitation will not be successful in hemorrhagic shock without control of bleeding. In many cases, the source of bleeding will be obvious. Significant bleeding can occur in the chest, abdomen, retroperitoneum-pelvis, and long bones without obvious external bleeding. The most common injuries to cause hemorrhagic shock include pelvic or femur fracture; rupture of the liver, spleen, or kidney; and injury to large thoracic or abdominal vessels. A hemodynamically significant intracranial bleed is not possible, since the elevation in intracranial pressure would result in brain herniation before a significant volume of blood could be lost. Even in significant trauma, the cause of internal bleeding may not be obvious. In these cases, a systematic workup is essential and includes the following:

- Chest radiograph to evaluate for hemothorax.
- Pelvis radiograph: The diagnosis of pelvic fracture should raise suspicion for pelvic or retroperitoneal bleeding. This may require definitive treatment with angiography.
- FAST examination: A positive FAST examination in the setting of trauma and hypotension typically mandates immediate surgical exploration in the OR.
- Extremity radiographs as indicated.

If the source of bleeding is still not identified and the patient is stable, a computed tomography scan is indicated.

The evaluation of nontraumatic bleeding follows a similar workup, because

significant bleeding can occur in the same locations as seen with traumatic bleeding. A pregnancy test is useful to rule out ruptured ectopic pregnancy. Chest radiographs can show evidence of aortic dissection or aneurysm. Ultrasound can be used as discussed above. Historical factors that may indicate retroperitoneal bleeding include anticoagulation or coagulopathy, femoral artery cannulation, or recent major surgery. Another potential source of nontraumatic hemorrhage is gastrointestinal bleeding. Rectal examination, nasogastric tube placement, and/or endoscopy will aid in the diagnosis.

Source Control

Bleeding can be controlled in a limited number of ways. For external bleeding, compression and pressure are the easiest and most efficient methods. For extremity bleeding, a tourniquet can be applied proximal to the injury if compression is not possible or effective. While the use of tourniquets remains controversial, experiences from the military and most recently with the Boston Marathon bombing have demonstrated their effectiveness. Guidelines from the Eastern Association of the Surgery of Trauma advocate tourniquet use as a level III recommendation. Available data show effectiveness in control of bleeding and improved survival when tourniquets are applied prior to the onset of shock compared with afterward. When available, a blood pressure cuff can be used as a tourniquet by applying the cuff proximal to the bleed and inflating above the systolic blood pressure. Tubing should be clamped with a hemostat to prevent inadvertent pressure loss, and the time of placement should be noted. Tourniquets can cause significant ischemia distal to the injury from both lack of arterial inflow and obstruction of venous outflow, so time of inflation should be limited to 2 hours, and tourniquets should be rapidly removed when definitive care can be established.

A traction splint can be applied to long bone fractures, typically femur fractures. This controls bleeding by realigning fracture fragments to reduce potential injury to adjacent vessels. In addition, it is thought that realigning the bone back to anatomical position will restore the normal circumference and length of the thigh, thus reducing the potential space into which bleeding could occur.

The use of tranexamic acid (TXA), an antifibrinolytic agent, in traumatic bleeding gained support after the Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial. This double-blinded, multicenter, randomized controlled trial involving more than 20,000 patients looked at the effect of TXA in patients with blunt or penetrating trauma. Results showed that

the treatment group had decreased 28-day mortality from any cause and from bleeding. The greatest benefit was seen in patients with the most severe shock. No differences were found between the groups regarding the number of vaso-occlusive events, need for transfusion, and need for surgery. Subgroup analysis showed that the benefit was greatest if TXA was given less than 1 hour from injury and that TXA may cause harm if given 3 hours after injury.

Volume

Crystalloids

IVFs are the mainstay of resuscitation. Crystalloid fluid contains only electrolytes and small molecules; it is inexpensive, easily stored, and readily available. Crystalloid can be infused quickly given its low viscosity and is given to restore blood volume in order to restore perfusion. In the case of intravascular fluid loss (not bleeding) or limited and controlled bleeding, restoring intravascular volume and thus increasing cardiac output will increase tissue perfusion. In these settings, IVFs should be the first-line treatment with an initial 2-L fluid bolus as recommended by advanced trauma life support (ATLS) guidelines. For the critically ill patient with uncontrolled bleeding, the basis for the use of IVFs as resuscitation has been challenged.

Crystalloid resuscitation gained support during the Vietnam War era with the work of Shires and others.[1] They suggested that a significant deficit in interstitial volume developed that was disproportionate to the intravascular volume loss and could be corrected with fluid administration equal to 3 (or even 8 in severe cases) times the estimated blood loss. This large-volume resuscitation improved rates of renal failure as well as survival during the Vietnam War. However, this resulted in an increased incidence of respiratory failure, first termed “Da Nung lung” (now known as acute respiratory distress syndrome), which continues to be a major cause of morbidity and mortality in trauma patients today. In addition, large-volume resuscitation with normal saline showed increased mortality and hyperchloremic metabolic acidosis in animal studies, which led the ATLS program to propose lactated Ringer’s solution as the fluid of choice in resuscitation.

A clear benefit to immediate large-volume fluid resuscitation has not been demonstrated in trauma patients. In the 1990s, two landmark studies questioned the role of IVF resuscitation in trauma patients. The first, by Bickell et al[2], randomized patients with penetrating torso trauma to either immediate or

delayed fluid resuscitation. The delayed group received significantly less fluid and had significantly improved mortality and a shorter hospital length of stay. The second study, by Dutton et al[3], randomized patients to receive IVFs to a systolic blood pressure goal of greater than 100 mm Hg or greater than 70 mm Hg. The investigators found no change in mortality between the groups, but time to control of bleeding was significantly longer in the 100-mm Hg group.

Basic science research has shown that resuscitation fluid alone can activate inflammatory and immune cascades, compounding cytotoxicity caused by the initial insult. Because crystalloid contains only small molecules, it can freely cross cell membranes. The majority of fluid administered (up to 80%) will shift from the intravascular space to the interstitial space within minutes, contributing to pulmonary volume overload and abdominal compartment syndrome with large-volume resuscitation. The fluid can also worsen acidosis and hypothermia.

Both beneficial preclinical trials and pathophysiological rationales during the last decade brought significant interest in the use of hypertonic solutions for early resuscitation. Hypertonic solutions cause redistribution of water from the extravascular to the intravascular space, which in theory could restore intravascular volume and avoid the negative consequences of large-volume resuscitation. In addition, hypertonic solutions may exert anti-inflammatory and immunomodulatory effects that could be beneficial in critically ill patients. Unfortunately, large-scale studies failed to demonstrate a benefit of hypertonic solutions, and so their use cannot be advocated as part of routine resuscitation.

Colloids

Colloid fluid contains large molecules such as human albumin or high-molecular-weight glucose polymers. The theoretical advantages over crystalloids include slower redistribution from the intravascular to the extracellular space due to high oncotic pressure, ability to draw additional fluid into the intravascular space, and anti-inflammatory and antiapoptotic effects. However, colloids also have several disadvantages. In times of altered capillary permeability, such as during inflammation or infection, albumin is more freely moveable and oncotic force becomes less important than hydrostatic force, so the beneficial effect of colloids remaining in the intravascular space is likely diminished or lost in critically ill patients. Colloids are significantly more expensive and are more difficult to store. The synthetic colloids have many potentially dangerous side effects, including the activation of inflammatory cascades. Hydroxyethyl starch inhibits platelet function and can cause significant coagulopathy and kidney

injury. Dextran also increases bleeding tendencies and is nephrotoxic. Albumin, the most commonly used colloid fluid, contains human albumin and will likely not be accepted by patients who will not accept blood product transfusion.

The crystalloid versus colloid controversy is long-standing. Although numerous randomized controlled trials have compared crystalloids and colloids, these trials generally have not targeted patients exclusively with hypovolemic-hemorrhagic shock. A comprehensive review of these studies is outside the scope of this chapter, but there is no compelling evidence suggesting that patients in hypovolemic or hemorrhagic shock should receive resuscitation with colloids.

Blood Products

Transfusion of fresh whole blood (FWB) to patients in severe hemorrhagic shock requiring massive transfusion makes theoretical sense—the patient gets back what he or she lost in the correct ratio. Although FWB offers distinct advantages, experience with it is limited to animal studies and the military. FWB has a higher concentration of platelets, RBCs, fibrinogen, and clotting factors compared with blood component therapy. About 500 mL of FWB has a hematocrit of 38% to 50%, a platelet count of 150,000 to 400,000, fibrinogen of 1,500 mg, and 100% coagulation function; above all, FWB is warm. In contrast, the combination of 1 unit of RBCs, 1 unit of platelets, 1 unit of fresh frozen plasma, and a ten-pack of cryoprecipitate is 660 mL; it has a hematocrit of 29%, platelet count of 87,000, fibrinogen of 750 mg, and 65% coagulation function, and it needs to be warmed prior to transfusion. Just as IVF can contribute to worsening acidosis and coagulopathy, so can inappropriate blood transfusion. Furthermore, blood products, especially RBCs, may lose potency as the cells age, although this is controversial.

Patients in hemorrhagic shock with ongoing bleeding need treatment for both anemia and coagulopathy. This led to the concept of massive transfusion protocols to guide such transfusion in severe bleeding. Massive transfusion is usually defined as more than 10 units of blood transfused in 24 hours, although this definition is evolving. It is guided by the principles that correcting coagulopathy is just as important as maintaining oxygen-carrying capacity. Further, patients with active bleeding have rapidly changing physiological parameters, so traditional laboratory tests to determine transfusion needs are of very limited utility. Early data from the Joint Theater Trauma Registry showed that the closer the ratio of fresh frozen plasma to RBC was to 1:1, the greater were the improvements in injury severity scores and mortality. Recent data

regarding optimal transfusion ratios favor as close to 1:1:1 (plasma to platelets to RBCs) as possible. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial was a multicenter, unblinded, randomized controlled trial comparing a 1:1:1 to a 1:1:2 transfusion protocol in patients with severe trauma. No significant differences were found in 24-hour and 30-day mortality rates. However, mortality was reduced within the first 24 hours due to exsanguination in the 1:1:1 group. Less evidence is available on how to transfuse cryoprecipitate in a massive transfusion protocol.

Resuscitation Strategies

The clinician must recognize the distinctions between simple hypovolemic shock, controlled or minor hemorrhagic shock, and uncontrolled or severe hemorrhagic shock. In the former two conditions, management is more straightforward. Shock typically improves with volume replacement and simple blood product transfusion, assuming the source of volume loss is controlled. However, resuscitation principles differ in hemorrhagic shock. A commonly accepted standard set forth by ATLS calls for the infusion of blood if 2 L of crystalloid fails to reverse the signs of shock. However, there is a trend to transfuse blood even earlier if a patient responds only transiently or does not respond sufficiently to the first liter of fluid. Notably, resuscitation with IVF alone can worsen outcomes because it worsens coagulopathy, acidosis, hypothermia, and tissue edema. Fluid should be given selectively, in lower volumes, and should be warmed.

The aim of transfusing early is to help restore oxygen delivery to tissues and normalize coagulopathy. Of course, risks are associated with blood product transfusion, including immunosuppression, transfusion-related acute lung injury, transfusion reaction, and potential for disease transmission. A critical consideration is that resuscitation is not a substitute for hemorrhage control; rather, resuscitation should support the patient until bleeding is controlled.

Hypotensive Resuscitation or Permissive Hypotension

The idea of permissive hypotension was first set forth in 1918 by Cannon[4] with the goal of maintaining the blood pressure low enough that thrombus can form to achieve hemostasis but still high enough to perfuse vital organs. Increasing hydrostatic pressure, especially in the setting of worsening coagulopathy, can dislodge early soft clots and increase bleeding. This is also known as the “pop the clot” theory. The transient increase in blood flow from fluid resuscitation can

also cause reperfusion injury because increased blood flow brings increased levels of circulating toxins produced by initial ischemic injury and subsequent inflammation. The goal of treatment is directed by clinical end points (eg, appearance of a radial pulse, improvement in mental status) combined with direct blood pressure goals. Care should be taken with patients who are hypertensive at baseline or patients who have severe cerebrovascular disease, as they may not tolerate lower or even "normal" blood pressures.

Hemostatic Resuscitation

One of the most important goals of resuscitation is to correct coagulopathy and limit blood loss. Hemostatic resuscitation calls for early transfusion of blood components in a ratio that closely resembles whole blood, as opposed to IVFs, to restore both perfusion and normal coagulation function.

Damage Control Resuscitation or Delayed Resuscitation

This strategy combines elements of the strategies described previously. The patient is kept warm and permissive hypotension is allowed until definitive hemostasis can be achieved in the OR. Hemostatic resuscitation is performed by minimizing the use of IVFs via early transfusion of products in 1:1:1 ratio or of FWB when possible. Patients should be rapidly transported to the OR for damage control. Damage control entails performing an abbreviated laparotomy to control bleeding and contamination and to restore blood flow. Then the patient is packed, provided with a temporary closure, and transferred to the ICU for rewarming, correction of acidosis, reversal of coagulopathy, and optimization of hemodynamics and ventilation prior to definitive surgical repair after physiological parameters have been met.

These resuscitation strategies have 2 major caveats: (1) they are not meant for the management of patients with concomitant severe brain injuries since any decrease in blood pressure will decrease cerebral perfusion pressure and can worsen outcome significantly, and (2) they are not meant for patients in whom bleeding is controlled or is mild.

SUMMARY

Hypovolemic and hemorrhagic shock states result in profound alterations in oxygen delivery and tissue perfusion. While resuscitation strategies continue to evolve, management of patients in shock requires a complete and rapid

assessment, use of appropriate laboratory and imaging studies, source control, and timely and individualized volume replacement.

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CHAPTER 11

Acute Myocardial Infarction and Acute Coronary Syndromes

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Key words: acute ST-segment elevation myocardial infarction, non-ST elevation acute coronary syndrome, reperfusion therapy, risk stratification, vulnerable plaque, primary coronary intervention, thrombolytic therapy

EPIDEMIOLOGICAL CHARACTERISTICS

Acute coronary syndromes (ACSs) arise as complications of chronic coronary artery atherosclerosis. ACS is classified into 2 clinical syndromes: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS), the latter of which includes the prior designations non-ST segment elevation acute myocardial infarction (NSTEMI) and unstable angina (UA). Comprehensive care guidelines from the American College of Cardiology Foundation and the American Heart Association have recently been updated and published.[1,2]

These conditions occur commonly. In the United States in 2009, there were 683,000 hospitalizations for ACS, 25% to 40% of which were STEMI. Thirty percent of ACSs occur in women and 13.3% in non-Caucasian populations.[3] Twenty-three percent of ACS patients have diabetes, and these diabetic patients have an overall worse prognosis. In-hospital mortality is 5% to 6%, and 1-year mortality after ACS is 7% to 18%. In 2016 it is estimated that 550,000 myocardial infarctions (MIs) will occur in patients without a history of MI, with an additional 200,000 recurrent MIs. The average age of a first MI is 65.1 years in men and 72 years in women.[4] The frequency of MI has decreased over the past 2 decades.

PATHOGENESIS

Coronary atherosclerosis is a process in which lipids, fibrotic tissue, and smooth muscle and inflammatory cells infiltrate the arterial wall. Early in the formation of the atherosclerotic plaque, the artery remodels and the outer circumference becomes larger.[5] As the atheroma progresses, stenosis of the artery lumen occurs. Most ACSs are caused by disruption of this plaque, which leads to intraluminal thrombosis and occlusion of the artery. Characteristics of a "vulnerable plaque," that is, a plaque more likely to cause ACS, include a large lipid-rich core, activated intimal smooth muscle cells and macrophages, and a thin fibrous cap separating the plaque from the arterial lumen. Triggers of plaque rupture include physical exertion and mental stress, but rupture often occurs without a specific precipitator. Whereas 75% of acute MIs are thought to be initiated by plaque rupture, about 25% may be due to plaque erosion, in which the atherosclerotic process results in loss of arterial endothelium and exposure of the intima to contents of circulating blood. Plaque erosion is more common in ACS occurring in younger women and is associated with cigarette smoking.[6] Plaque rupture and erosion lead to release of tissue factor, proinflammatory substances, and procoagulants. Intraluminal coronary thrombosis occurs as a result of activation, adhesion, and aggregation of platelets and deposition of thrombin and fibrin. Spontaneous coronary dissection is a rare cause of ACS.

CLASSIFICATION OF ACUTE MYOCARDIAL INFARCTION

A consensus document classifies MI into 5 main types[7]:

- Type 1—Spontaneous MI related to ischemia due to a primary coronary event, such as plaque rupture, erosion, or dissection, leading to intraluminal thrombosis.
- Type 2—MI secondary to ischemic imbalance caused by increased oxygen demand (eg, anemia, tachyarrhythmias, bradyarrhythmias, sepsis, respiratory failure, severe hypertension or hypotension) or decreased supply (eg, coronary artery spasm or embolism).
- Type 3—Sudden, unexpected cardiac death with symptoms suggestive of myocardial ischemia, accompanied by electrocardiographic (ECG) changes such as new ST-segment elevation or new left bundle-branch block, without abnormal biomarker values. In these patients, death occurs before blood samples can be obtained or before the increase in biomarkers can be

detected. Coronary thrombosis may be demonstrated at angiography or autopsy.

- Type 4—Associated with a percutaneous revascularization procedure:
  - Type 4a—MI associated with a coronary stenting procedure.
  - Type 4b—MI related to coronary stent thrombosis as documented by angiography or at autopsy.
- Type 5—MI associated with coronary artery bypass graft surgery.

GENERAL APPROACH TO THE PATIENT WITH ACS

Most patients with ACS will present with chest discomfort lasting 30 minutes or longer. Typically, the discomfort is described as dull, tight, or pressure-like, and it may radiate to the neck, jaw, or left arm. However, about one-third of patients will present with symptoms other than chest discomfort, including epigastric discomfort, nausea and vomiting, diaphoresis, dyspnea, and generalized weakness. Women often experience nontypical symptoms with ACS.

The average time of presentation after onset of symptoms is 120 to 180 minutes.[4] The general population should be educated that early presentation to an emergency facility is strongly recommended when symptoms suspicious for acute coronary ischemia occur, because earlier treatment of ACS results in higher survival rates. Transport to a hospital by emergency squad, and not by family members, also is strongly recommended. Specific therapies can be initiated sooner if emergency medical services perform a prehospital ECG and appropriate patients are transported directly to hospitals that can perform coronary interventions emergently.

After the patient arrives in the emergency department, it is mandatory that a 12-lead ECG be performed and interpreted within 10 minutes. If new ST-segment elevation is present, then STEMI is diagnosed and emergency reperfusion strategies are initiated (see below). New ST-segment depression on ECG increases the likelihood of NSTE-ACS. If the initial ECG is not diagnostic and the patient continues to experience chest discomfort, repeating the ECG, as often as every 10 minutes, may aid in timely diagnosis. In patients with ST-segment elevation in the inferior leads, performing an ECG with right precordial leads (V_3R, V_4R) may show ST-segment elevation, aiding in the diagnosis of right ventricular infarction. Extending the left precordial chest leads to record signals

from left posterior axilla and posterior left chest ($V_{7\text{-}9}$) may help make a diagnosis of acute inferior-lateral infarction caused by acute occlusion of the circumflex coronary artery.

The first step in taking the patient's history is assessing the likelihood that the presenting symptoms are indeed due to ACS. Clinicians should take note of a known history of coronary artery disease and the presence of coronary artery disease risk factors, including diabetes mellitus, cigarette smoking, hypertension, hyperlipidemia, and a family history of premature coronary disease in a first-degree relative. During the physical examination, clinicians should look for signs of complications of ACS, including tachycardia or arrhythmia, hypertension or hypotension, pulmonary congestion, low cardiac output, or new cardiac murmurs. Risk factors for abnormal bleeding are also important to determine.

Urgent laboratory evaluation includes complete blood cell count, blood chemistries, and determination of serum troponin. Troponin is now the preferred biomarker for the diagnosis of acute MI. Troponin is more sensitive and more specific than serum CK-MB for diagnosis of ACS. Troponin elevation can be seen in conditions other than acute MI due to coronary artery disease, such as myocarditis, chronic heart failure, acute cardiomyopathy, and chronic kidney disease. However, in a clinical setting suspicious for ACS, elevation of troponin is diagnostic of acute myocardial necrosis. The diagnosis of STEMI should be made on the basis of the ECG and clinical signs and symptoms before biomarker results are reported, so that reperfusion therapies can be instituted rapidly.

Supplemental oxygen should be administered only for documented hypoxemia.[1] A trial of sublingual nitroglycerin can be used to relieve discomfort, in the absence of hypotension or tachycardia. Morphine sulfate in low doses can be used for analgesia.

Many communities are now establishing regional systems for the rapid assessment of patients with suspected ACS in the field. These emergency medical system teams can perform a 12-lead ECG at the scene and transmit the results wirelessly to the regional medical center. Improvements in systems of care that lead to more rapid diagnosis of and appropriate therapy for patients with acute MI are likely to lead to improved survival rates.[8,9]

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

In the large majority of patients, STEMI is caused by acute thrombotic occlusion

of an epicardial coronary artery. The goal of therapy is to establish reperfusion of the artery as quickly as possible. More rapid patency of the infarct-related artery is associated with less myocardial necrosis, smaller infarcts, improved survival, less left ventricular dysfunction, and a decreased incidence of chronic heart failure and long-term ventricular arrhythmia. In the initial assessment of the patient, prompt diagnosis of STEMI is paramount. ECG diagnosis of STEMI is based on new, persistent ST-segment elevation at the J point in leads V_3 and V_4 of at least 2 mm in men and 1.5 mm in women, or at least 1 mm in 2 other contiguous chest or limb leads.[1] If new left bundle-branch block is present, other confirmatory diagnostic tests are indicated, such as a new left ventricular wall motion abnormality on echocardiography. ECG findings that may mimic STEMI include early repolarization normal variant, left ventricular hypertrophy, myopericarditis, transient apical ballooning syndrome, or Brugada syndrome[10] (**Figure 1**). Once STEMI is diagnosed, 2 emergency reperfusion therapies are indicated—emergency coronary balloon angioplasty with stenting (primary percutaneous intervention, or PCI) or intravenous administration of a thrombolytic agent. Although primary PCI is the preferred treatment, the decision of which therapy to use depends on how quickly the patient can be transported to a cardiac catheterization laboratory and the presence of medical conditions that increase the risk of bleeding complications after thrombolysis.

Figure 1. (a) Tracing 1 shows normal ST segment elevation in the precordial leads. Tracing 2 shows early repolarization normal variation, with notching at the J point in leads V3 and V4.

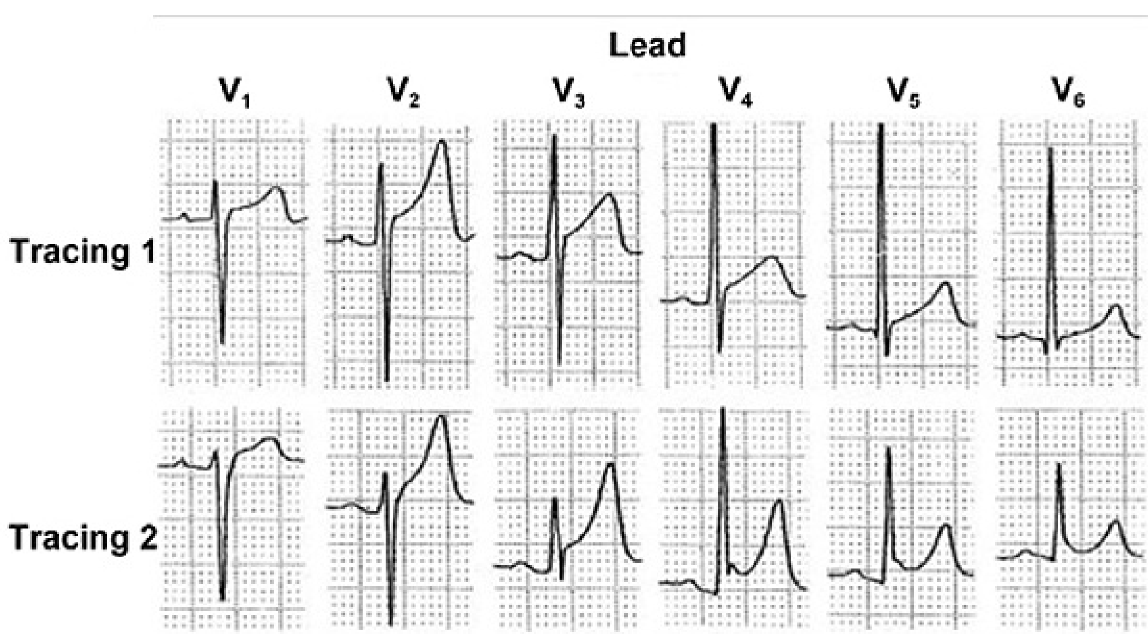
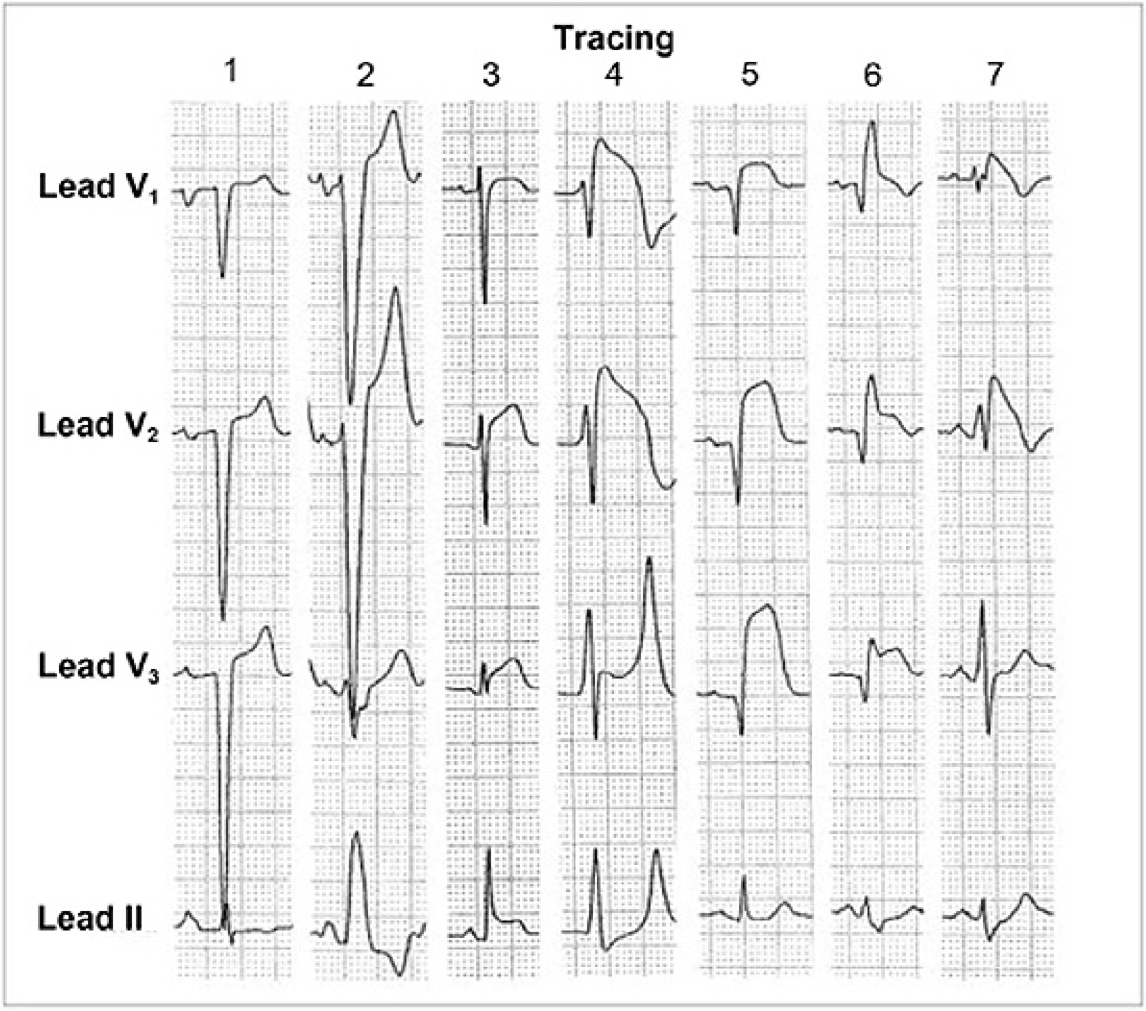


Figure 1. (b). Abnormal ST elevation in various conditions



Tracing 1: Left ventricular hypertrophy. Tracing 2: Left bundle branch block. Tracing 3: Acute pericarditis. Tracing 4: Hyperkalemia. Tracing 5: Acute anterior wall STEMI. Tracing 6: Acute anterior wall STEMI with right bundle branch block. Tracing 7: Brugada syndrome.

Reproduced with permission Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med.* 2003; 349(22):2128-2135.

All eligible patients with symptom onset of 12 hours or less prior to medical contact should be treated with reperfusion therapy. In patients with symptom duration of 12 to 24 hours, emergency PCI should be considered if symptoms are ongoing. Current standards for treatment of STEMI include that the time from first medical contact to initial intracoronary device therapy should be less than 90 minutes. If a patient initially presents to a PCI-capable hospital, the time from arrival to device therapy ("door-to-balloon time") should be 60 minutes or less. In patients treated with thrombolysis, time from initial medical contact to the start of thrombolytic infusion or injection should be less than 30 minutes ("door-to-needle time"). In the National Registry for Myocardial Infarction (NRMI)

database, a door-to-balloon time of less than 90 minutes was associated with a mortality rate of 3%, whereas a door-to-balloon time greater than 150 minutes resulted in 7.4% mortality.[11] Similarly, a door-to-needle time of less than 30 minutes resulted in a 2.9% mortality, and mortality increased to 6.2% if this time was greater than 45 minutes.[12]

PCI for STEMI

Many trials have been examined emergency coronary angioplasty and stenting (primary PCI) compared with thrombolysis for treatment of STEMI. Restoring patency of the infarct-related artery occurs more frequently with PCI. A meta-analysis of 23 trials confirmed that mortality rate with primary PCI was 7%, whereas the mortality rate for thrombolysis was 9%. The occurrence of recurrent ischemia and reinfarction is lower with PCI than with thrombolysis (3% vs 7%, respectively), and the incidence of stroke is lower (1% vs 2%, respectively); further, bleeding complications are less frequent with PCI.[13] It is estimated that PCI saves 70 lives out of 1,000 patients treated and that it saves 20 lives more per 1,000 patients treated compared with thrombolysis. PCI results in successful reperfusion in 90% to 95% of cases.[14,15]

If a patient with STEMI presents to a hospital that is capable of performing PCI quickly, then this is the preferred therapy. PCI should be performed by experienced, capable interventional cardiologists, and provisions for emergency heart surgery should be in place, given the possibility for severe complications. If a patient presents to a hospital without PCI capability, then the decision whether to transfer to a PCI center or treat with thrombolytic therapy is determined by 4 factors: (1) time of onset of symptoms; (2) the patient's risk of bleeding complications with thrombolysis; (3) whether transfer time will be less than 120 minutes, where *transfer time* is defined as the time from arrival at the initial hospital to performance of PCI at the referral hospital; and (4) whether the patient demonstrates features predicting a "high-risk" MI (see below). Because thrombolysis is most effective when administered within 2 to 3 hours of the onset of symptoms, strong consideration should be given to thrombolysis for patients who present within this time frame and if transfer time to a PCI center is expected to exceed 60 minutes. If transfer time is shorter, then either transport for PCI or thrombolysis is an acceptable therapy. If patients present more than 3 hours after onset of symptoms, transfer for PCI is recommended and should be accomplished rapidly (a "door-in, door-out time" of 30 minutes). If patients have a contraindication to thrombolysis, then transfer for PCI is mandated.[1,2]

Transferring patients with STEMI to a PCI hospital has been demonstrated to be safe, with reported transfer complication rates of 0.5% mortality and 1.4% to 2.3% serious arrhythmia or heart block.[16,17]

Patients who show signs of a high-risk MI also have better outcomes with PCI. Included in this group are elderly patients, patients with anterior wall STEMI, and those with serious ventricular arrhythmia, systolic blood pressure less than 100 mm Hg, signs of acute heart failure or low cardiac output, or cardiogenic shock.[18] Last, if the ECG suggests STEMI but the diagnosis is not definitive, emergency coronary angiography is preferred to administration of lytic therapy (**Table 1**).

Table 1. Algorithm to Determine the Best Treatment Strategy to Achieve Reperfusion in Patients with STEMI

Criteria for Transfer for Percutaneous Intervention	Criteria for Administration of Thrombolytic Agent Within 30 Minutes of Arrival
1. The patient can be transported out within 30 min ("door-in, door-out time") and can begin intervention within 120 min of first medical contact. 2. The patient has a high risk of bleeding complications with thrombolytic therapy. 3. Ischemic symptoms continue for 12-24 h. 4. The patient has cardiogenic shock or systolic blood pressure <100 mm Hg. 5. Other high-risk features are present: anterior infarction, old age, severe ventricular arrhythmia, severe heart failure. 6. Evidence indicates failed reperfusion following thrombolytic therapy.	1. The anticipated time for transfer to hospital for percutaneous intervention is >120 min. 2. Optional for patients who present soon after onset of symptoms (1-2 h).

Immediately prior to balloon angioplasty and stenting, aspiration of the intracoronary thrombus is recommended.[19,20] Use of either a bare metal stent or a drug-eluting stent is indicated, as no significant difference between types of stent in terms of survival or rate of recurrent infarction has been found. The advantage of using a drug-eluting stent is a reduction in the rate of subsequent target vessel revascularization. The disadvantage of a drug-eluting stent is the need for treatment with 2 antiplatelet agents for 1 year, whereas a bare metal stent requires only 1 month of antiplatelet therapy. A bare metal stent should be

used if patients are determined to have a high bleeding risk, if adherence to 1 year of dual antiplatelet therapy (DAPT) is predicted to be poor, or if the need for a noncardiac surgery or procedure is known to be imminent.[1]

Anticoagulant therapy should be used as supportive therapy for primary PCI. The recommended agents are unfractionated heparin or bivalirudin.

Patients undergoing primary PCI for STEMI should receive DAPT prior to the procedure: aspirin 160 to 325 mg and an oral loading dose of a second agent, either clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. Clopidogrel is continued at 75 mg daily, prasugrel at 10 mg daily, and ticagrelor at 90 mg twice daily. The maintenance dose of prasugrel is decreased to 5 mg daily in patients weighing less than 60 kg. Prasugrel is associated with a higher bleeding rate than clopidogrel and is contraindicated in the setting of prior stroke, prior transient ischemic attach, or active bleeding. Prasugrel should not be used in patients older than 75 years, patients who weigh less than 60 kg, or patients who are at high risk of bleeding. The preferred maintenance dose of aspirin is 81 mg daily, and this is the mandated dose when used with ticagrelor. DAPT is continued for 1 year following ACS.[21-25]

In patients who receive DAPT prior to primary PCI, routine administration of a glycoprotein IIb-IIIa inhibitor carries no additional benefit. These medications can be administered on an individual basis, such as when loading with DAPT is delayed or if a large intracoronary thrombus burden is seen at angiography. The 3 available glycoprotein IIb-IIIa inhibitors that can be used are eptifibatide, tirofiban, and abciximab.[26]

Thrombolytic Therapy for STEMI

The majority of patients with STEMI present to hospitals that do not have PCI capability. Therefore, thrombolytic therapy remains an important treatment option. Thrombolytics convert plasminogen to plasmin, which then breaks down fibrin and fibrinogen within the thrombotic coronary occlusion, reestablishing vessel patency. The sooner thrombolytics are administered after the onset of STEMI, the more likely reperfusion will occur. Overall, thrombolytic therapy accomplishes complete reperfusion in 60% to 70% of cases. Thrombolytics should be administered within 30 minutes of presentation to hospital.

Several large, randomized controlled clinical trials demonstrated significant mortality benefit with thrombolytic therapy compared with conventional

therapy.[27-30] It is estimated that 50 lives are saved for every 1,000 patients treated.[14,15] In large trials, the rate of death plus nonfatal stroke averaged 7%. The major complication of therapy is intracranial hemorrhage, which occurs in 0.5% to 1.5% of patients. Intracranial hemorrhage in this setting has an 80% mortality rate. Factors that increase the risk of intracranial hemorrhage include advanced age, female sex, weight under 70 kg, and hypertension. Although the risk of bleeding complications is higher in elderly patients, the benefits of therapy are also greater.

Thrombolytic therapy results in a very high reperfusion rate if administered in less than 1 hour from symptom onset, and this therapy can be prescribed if patients have been symptomatic for up to 12 hours. Treatment at 12 to 24 hours after symptom onset can be considered in patients with continued chest pain and ST-segment elevation on ECG. Treatment administered more than 24 hours after symptoms onset is not beneficial. Thrombolytic therapy is not indicated in patients with NSTE-ACS.

Absolute contraindications to thrombolytic therapy include a history of intracranial hemorrhage or arterial-venous malformation, cerebral aneurysm, or malignancy. Additional absolute contraindications include cerebrovascular accident within the prior 3 months, active bleeding, suspected aortic dissection, and significant closed-head trauma within the prior 3 months. Relative contraindications include a history of severe hypertension or current blood pressure greater than 180 mm Hg systolic or greater than 110 mm Hg diastolic, prior cerebrovascular accident, current illness associated with more than 10 minutes of cardiopulmonary resuscitation, recent major surgery or bleeding episode, pregnancy, active peptic ulcer disease, noncompressible vascular puncture, or current anticoagulation therapy (**Table 2**).

Table 2. Absolute and Relative Contraindications for Thrombolytic Therapy

Absolute Contraindications	Relative Contraindications
Any prior intracranial hemorrhage	History of chronic, severe, poorly controlled hypertension
Known structural cerebral vascular lesion (eg, arteriovenous malformation)	Significant hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
Known malignant intracranial neoplasm (primary or metastatic)	Prior ischemic stroke >3 mo
Ischemic stroke within 3 mo (*except* acute ischemic stroke within 4.5 h)	Dementia
Suspected aortic dissection	Known intracranial lesion not covered in absolute contraindications
Active bleeding or bleeding diathesis (excluding menses)	Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
	Major surgery (<3 wk)

Significant closed-head or facial trauma within 3 mo Intracranial or intraspinal surgery within 2 mo Severe uncontrolled hypertension (unresponsive to emergency therapy) For streptokinase, prior treatment within the previous 6 mo	Recent (within 2-4 wk) internal bleeding Noncompressible vascular punctures Pregnancy Active peptic ulcer Oral anticoagulant therapy

Reproduced with permission Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004; 44(3):671-719.

Four thrombolytic agents are approved for clinical use. Streptokinase was the first agent shown to be beneficial and is the least expensive drug. However, it is administered as an infusion and can cause severe allergic reactions. Tissue plasminogen activator (tPA, alteplase) is more selective for clot-bound fibrin and has been shown to have a slight mortality benefit compared with streptokinase. Alteplase is also administered by infusion. The newer agents reteplase (rPA) and tenecteplase (TNK) have the advantage of bolus administration and are as effective as tPA (**Table 3**).

Table 3. Comparison of Intravenous Thrombolytic Agents for Treatment of Acute ST-Segment Elevation Myocardial Infarction

	Streptokinase	**Alteplase (tPA)**	**Reteplase (rPA)**	**Tenecteplase (TNK) (dosed according to body weight)**	
Dose	1.5 million units over 30-60 min	15-mg bolus, then 0.75 mg/kg over 30 min (max 50 mg), and then 0.5 mg/kg over 1 h (max 35 mg)	Two 10-unit boluses, 30 min apart	<60 kg 60-69 kg 70-79 kg 80-89 kg >89 kg	30 mg 35 mg 40 mg 45 mg 50 mg
Immunogenicity	Yes	No	No	No	
Half-life	23 min	4-6 min	18 min	20 min	
Fibrin specificity	– –	++	>	+++	
90-min patency	50%	75%	60%-70%	75%	

Note: — denotes not specific for thrombus-associated fibrin; > denotes low specificity for thrombus-associated fibrin; ++ denotes moderate specificity for thrombus-associated fibrin; +++ denotes high specificity for thrombus-associated fibrin.

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The rate of reinfarction in the early period after thrombolytic therapy is 10% to 20%. Therefore, all patients should also receive aspirin 162 to 325 mg as early as possible and then 75 to 162 mg daily. Clopidogrel is also indicated to maintain infarct artery patency. A loading dose of 300 mg is given to patients younger than 75 years, and the daily dose is 75 mg.[31,32] Anticoagulants should be administered for a minimum of 48 hours after thrombolytic therapy if PCI is not performed. Unfractionated heparin, enoxaparin, or fondaparinux can be used if there are no contraindications.

It is very important to assess whether thrombolytic therapy has restored coronary patency. Signs of successful reperfusion include prompt relief of chest discomfort, reduction of ST elevation by 70% in the ECG lead with the highest initial elevation at 60 to 90 minutes after administration, and the presence of reperfusion arrhythmias such as accelerated idioventricular rhythm. Immediate transfer for "rescue PCI," that is, emergency PCI performed after failed thrombolytic therapy, has been shown to reduce the risk of subsequent heart failure and to decrease the risk of reinfarction at the expense of a slight increase in the risk of stroke and bleeding. A trend toward improved survival has been seen with rescue PCI.[33]

The combination of thrombolytic therapy at half dose or full dose followed by routine urgent PCI, so-called facilitated PCI, has been studied in randomized trials. These have not shown improved outcomes when compared with PCI alone, and facilitated PCI may be associated with adverse outcomes.[34-36]

If thrombolytic therapy is successful, then early coronary angiography (within 24 hours) and PCI (if indicated) are recommended. In a meta-analysis of 7 randomized controlled clinical trials, early routine cardiac catheterization following successful thrombolysis was associated with significant improvement in the rates of death or recurrent MI at 30 days and 1 year.[37,38] Urgent catheterization is also indicated following successful thrombolysis if (1) patients develop recurrent ischemic symptoms, heart failure, or significant ventricular

arrhythmia; (2) significant ischemia is seen on stress testing in the recovery phase; or (3) patients develop hemodynamic instability or cardiogenic shock.

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES

Approach to the Patient

The pathogenesis and presentation of the prior designations *UA* and *NSTEMI* are closely related and can be grouped together as NSTE-ACS. Pathogenesis involves disruption of a coronary atherosclerotic plaque with subsequent platelet activation and aggregation, thrombus formation, and coronary vasoconstriction. Myocardial necrosis in this setting is caused by distal coronary embolization of platelet aggregates.

NSTE-ACS is diagnosed when patients develop symptoms of coronary ischemia at rest or with minimal exertion, often lasting more than 20 minutes. It may be a patient's first experience of coronary artery disease, or it may represent a worsening of prior symptoms, with more frequent, severe, or prolonged discomfort or onset at rest rather than with exertion. Specific diagnostic criteria may be lacking at presentation; thus, initial assessment of the character and precipitators of chest discomfort is extremely important. Physical examination may uncover the precipitators of unstable symptoms (eg, anemia, hypertension, tachyarrhythmia) or can help diagnose conditions that mimic coronary ischemia, including pericarditis, acute aortic dissection, and pulmonary embolism. The 12-lead ECG may show ST-segment depression, transient ST elevation, T-wave abnormalities, or no diagnostic changes. Comparison with prior ECGs, when available, is essential. Repeating the ECG 15 to 30 minutes after an initial nondiagnostic ECG is recommended. The presence of ST-segment depression indicates a worse prognosis compared with T-wave inversions or the absence of acute changes.

Troponin T and troponin I are the preferred biomarkers for diagnosis of ACS. In NSTE-ACS, serum troponin may or may not be elevated. An increase in serum troponin occurs as a result of myocyte necrosis and will be seen 3 hours after onset of ischemic symptoms. If patients present sooner than 3 hours after onset of symptoms and the initial troponin level is normal, then a repeat measurement of troponin level in 3 to 6 hours is recommended for diagnosis of NSTE-ACS. An initial elevation and then decrease in serum troponin level over time is the expected pattern in acute infarction. Depending on the severity of elevation,

serum troponin will remain elevated for up to 14 days. Elevation of troponin confers a worse prognosis.[39] Chronic low-level elevation of troponin may be seen in conditions other than ACS, such as chronic heart failure and chronic kidney disease, and NSTE-ACS should not be diagnosed in these circumstances. Troponin elevation is diagnostic when there is an appropriate clinical setting (such as new onset of symptoms consistent with acute myocardial infarction, arrhythmia or hemodynamic abnormalities) and/or confirmatory ECG changes as well as the typical rise-and-fall pattern.

Initial therapy involves a trial of sublingual nitroglycerin to relieve chest pain and the immediate administration of 160 to 325 mg of aspirin. A loading dose of clopidogrel should be given as well. The next step is assessment of the patient's risk of developing recurrent ischemia, infarction, or other complications in order to determine the appropriate diagnostic and therapeutic strategy.

Early Coronary Angiography and Revascularization vs Conservative Medical Management

Many randomized trials have been performed comparing an "invasive strategy," consisting of routine early coronary angiography and revascularization when appropriate, to a "conservative strategy" of initial stabilization with medical therapy followed by angiography only in selected patients. In the absence of ST-segment elevation on ECG, emergency angiography has not shown benefit. However, the use of early angiography is associated with improvement in outcomes in high-risk patients, including improvements in mortality, rates of recurrent MI, and rates of rehospitalization. A meta-analysis of trials revealed a 25% relative reduction in all-cause mortality with an early invasive strategy (all-cause mortality of 4.9% with invasive strategy vs 6.5% with conservative strategy).[40]

Risk stratification is a critical aspect of the initial evaluation of a patient with NSTE-ACS. The Thrombosis in Myocardial Infarction (TIMI) group developed the TIMI risk score, which is valuable in defining short-term prognosis.[41] The score is determined by age, the presence of multiple coronary disease risk factors, a known diagnosis of coronary artery disease, new ST-segment depression on initial ECG, multiple anginal episodes in the 24 hours prior to presentation, use of aspirin during the preceding week, and elevation of serum troponin. A higher score predicts an increased likelihood of death, recurrent infarction, or severe recurrent ischemia (**Figure 2**). Troponin elevation and transient ST-segment changes during symptoms in and of themselves confer high

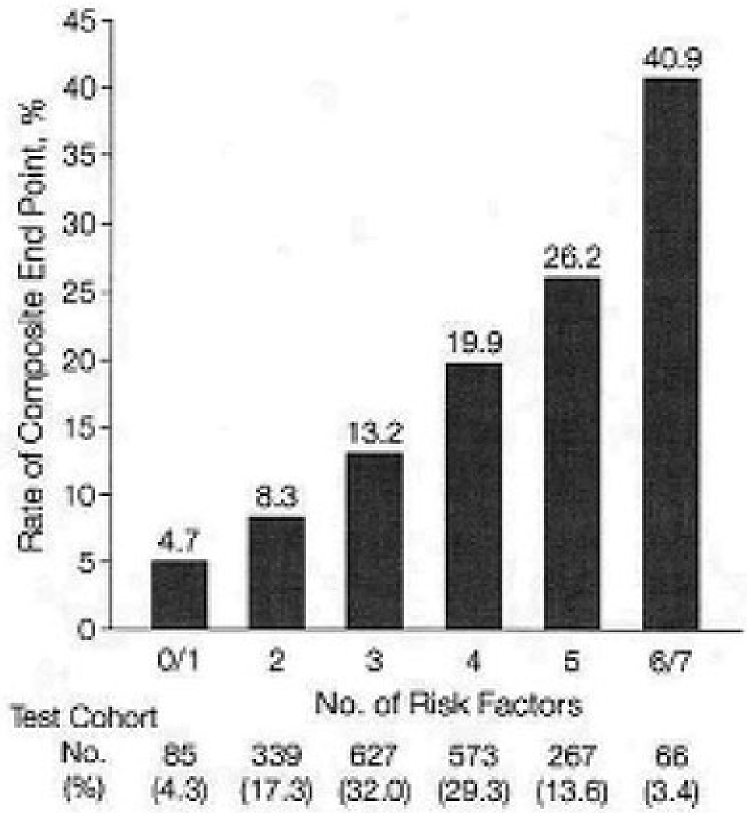
risk.

Figure 2. (a) The TIMI risk score

TIMI Rock Score
One point each for
1. Age >65 y
2. At least 3 risk factors for coronary artery disease
3. Known significant coronary artery disease
4. ST-segment depression
5. More than 1 anginal episode in last 24 h
6. Use of aspirin in last 7 d
7. Elevated troponin level

Reproduced with permission Antman EM, Cohen M, Bernick PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000; 284(7):835-842.

Figure 2. (b) Higher TIMI risk scores are associated with an increased risk of complications



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A risk score developed by the Global Registry of Acute Coronary Events (GRACE) investigators includes physical examination findings in the assessment. Tachycardia, hypotension, the presence of heart failure, and concomitant renal disease are included in the calculation. This score predicts the likelihood of mortality at 6 months after ACS (**Figure 3**).[42]

Figure 3. The GRACE risk score, used to determine 6 month mortality risk following hospitalization for acute coronary syndrome

Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 months.

Medical History

① Age in Years	Points
≤29	0
30–39	0
40–49	18
50–59	36
60–69	55
70–79	73
80–89	91
≥90	100

	Points
② History of Congestive Heart Failure	24
③ History of Myocardial Infarction	12

Findings at Initial Hospital Presentation

④ Resting Heart Rate, beats/min	Points
≤49.9	0
50–69.9	3
70–89.9	9
90–109.9	14
110–149.9	23
150–199.9	35
≥200	43

⑤ Systolic Blood Pressure, mm Hg	Points
≤79.9	24
80–99.9	22
100–119.9	18
120–139.9	14
140–159.9	10
160–199.9	4
≥200	0
	1
⑥ ST-Segment Depression	11

Findings During Hospitalization

⑦ Initial Serum Creatinine, mg/dL	Points
0–0.39	1
0.4–0.79	3
0.8–1.19	5
1.2–1.59	7
1.6–1.99	9
2–3.99	15
≥4	20

	Points
⑧ Elevated Cardiac Enzymes	15
⑨ No In-Hospital Percutaneous Coronary Invervention	14

Points

① ________

② ________

③ ________

④ ________

⑤ ________

⑥ ________

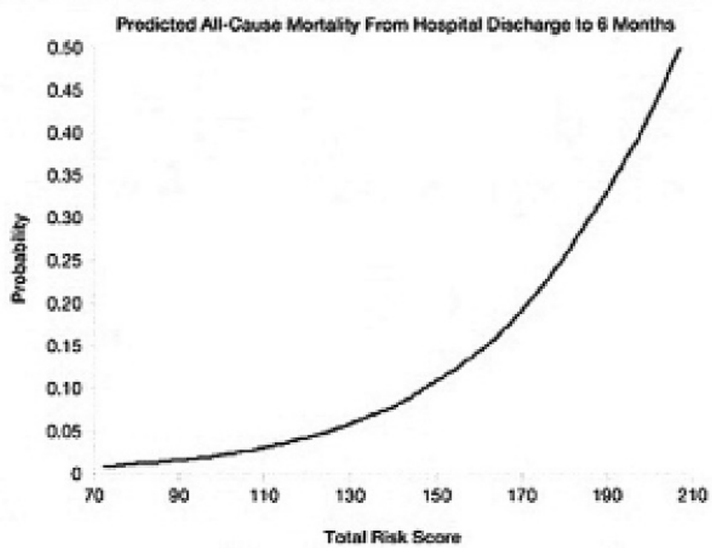
⑦ ________

⑧ ________

⑨ ________

Total Risk Score ________ (Sum of Points)

Mortality Risk ________ (From Plot)



Patient characteristics are listed in the top half of the figure, with the risk calculator at the bottom.

Reproduced with permission Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an

international registry. *JAMA.* 2004; 291(22):2727-2733.

The routine use of a risk assessment tool is a critical step in deciding on the appropriate diagnostic and treatment strategy. Patients with high risk scores should generally be evaluated with an early-invasive, early-revascularization approach. Urgent or early angiography is indicated in unstable patients, including those with heart failure or serious ventricular arrhythmia, those with recurrent ischemia, and stable patients with a high clinical risk score. In these high-risk patients, coronary angiography should be performed within the first 24 hours. An early conservative strategy is appropriate for low-risk patients, especially women.[43,44] However, in the absence of serious comorbidities, these patients should undergo early noninvasive testing for evaluation of left ventricular function and inducible ischemia. If testing shows a high-risk Duke treadmill score, large or multiple areas of ischemia, or significant left ventricular dysfunction, then angiography is indicated (**Table 4**).

Table 4. Patient Characteristics That Determine Whether Initial Conservative or Invasive Strategy Is Most Appropriate in Patients With UA/NSTEMI

Strategy	Status	Patient Characteristic
Invasive	Generally preferred	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
		Elevated cardiac biomarkers (TnT or TnI)
		New or presumably new ST-segment depression
		Signs or symptoms of HF or new or worsening mitral regurgitation
		High-risk findings from noninvasive testing
		Hemodynamic instability
		Sustained ventricular tachycardia
		PCI within 6 mo
		Prior CABG
		High-risk score (eg, TIMI, GRACE)
		Mild to moderate renal dysfunction
		Diabetes mellitus
		Reduced left ventricular function (LVEF <40%)
Conservative	Generally preferred	Low-risk score (eg, TIMI, GRACE)
		Patient or physician preference in the absence of high-risk features

Abbreviations: CABG, coronary artery bypass graft; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I; and TnT, troponin T

Reproduced with permission Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004; 44(3):671-719.

Antithrombotic Therapy for NSTE-ACS

Aspirin should be administered immediately at 162 to 325 mg and continued indefinitely at 75 to 325 mg daily. Clopidogrel is substituted in aspirin-intolerant patients. If an early invasive approach is used, DAPT with aspirin and clopidogrel or ticagrelor is recommended. Following successful PCI, DAPT with aspirin and clopidogrel, prasugrel, or ticagrelor is indicated for 1 year. A slight increase in bleeding is associated with the use of prasugrel. Side effects of ticagrelor include dyspnea and bradycardia.

Anticoagulation therapy is also started, using unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux.[45-48] In patients receiving unfractionated heparin, platelet counts should be monitored daily as there is a 0.2% risk of heparin-induced thrombocytopenia. Compared with unfractionated heparin, enoxaparin has a more consistent anticoagulant effect and a lower incidence of heparin-induced thrombocytopenia. The dose of enoxaparin needs to be lowered in patients with chronic kidney disease who have a creatinine clearance less than 30 mL/min. The factor Xa inhibitor fondaparinux has been shown to have favorable outcomes in UA/NSTEMI with fewer major bleeding complications. Bivalirudin is a direct thrombin inhibitor that can be used. Glycoprotein IIb-IIIa inhibitors can be considered for high-risk patients.

Warfarin is not indicated for patients with NSTE-ACS. The annual risk of bleeding complications in patients treated with warfarin is 2% to 3%; this risk rises to 4% to 6% when a single antiplatelet drug is added and to 10% to 14% when warfarin is added to DAPT ("triple therapy").[49] If patients have another indication for warfarin, such as chronic atrial fibrillation or venous thromboembolism, the combination of warfarin plus DAPT should be prescribed at the lowest effective dose for the shortest time feasible.

For stable patients treated with an initial conservative strategy, an evaluation of

left ventricular function with echocardiography and assessment of provocable ischemia with stress testing should occur during hospitalization in appropriate patients. Treadmill stress ECG can be performed in patients who are able to exercise and who have a normal resting ECG. Imaging with stress nuclear or stress echocardiography modalities should be conducted in patients who do not have an ECG that can be reliably interpreted during stress or who are unable to exercise on a treadmill. If left ventricular function is abnormal or if significant ischemia is seen on testing, coronary angiography should be strongly considered.

Medical Therapy for ACS

Several classes of medications have been shown to be of great benefit for patients with coronary artery disease following acute MI or ACS. These medications (1) reduce mortality during hospitalization and long-term follow-up; (2) improve recovery of abnormal left ventricular function and reduce the subsequent risk of heart failure; and (3) reduce the risk of recurrent coronary events by retarding the progression of coronary atherosclerosis. Patients should be discharged from the hospital on appropriate combinations of these medications, as it has been shown that prescriptions supplied at hospital discharge improve the rate of long-term adherence.

β-Blockers

β-Blockers blunt the effects of catecholamine stimulation of the heart, reducing heart rate, blood pressure, and contractility and decreasing oxygen demand. β-Blockers reduce the risk of serious ventricular arrhythmia and reinfarction and attenuate maladaptive left ventricular remodeling after infarction, and they are associated with improved mortality following MI. These drugs can be given intravenously in the acute stage of ACS in patients with tachycardia and hypertension. Oral administration of β-blockers should begin on day 1 of hospitalization for ACS, in the absence of second-degree or higher atrioventricular block and heart failure and if the patient is deemed to be at low risk for development of cardiogenic shock. β-Blockers should be prescribed for patients with heart failure after the condition has been stabilized. β-Blockers should be administered to older patients and even to patients with chronic lung disease without active bronchospasm.[50,51]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

These agents work as arterial dilators, lowering blood pressure, left ventricular afterload, and wall stress. They help to prevent adverse left ventricular remodeling after MI and also improve endothelial function. Angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease mortality from acute MI, reduce the risk of recurrent infarction, and reduce the incidence of heart failure.[52-55] Early intravenous administration carries no benefit. Oral ACE inhibitors should be started early in the hospital course for patients with acute anterior wall MI, left ventricular ejection fraction less than 40%, hypertension, and chronic kidney disease, as long as systolic blood pressure is higher than 100 mm Hg. These drugs should be continued after discharge. Angiotensin receptor blockers have similar indications and have been shown to confer equivalent benefits when given to patients who cannot tolerate ACE inhibitors.

Aldosterone Blockers

The aldosterone blocker eplerenone is indicated for patients after acute MI in the early convalescent phase (days 3-14) if left ventricular ejection fraction is less than 40% and diabetes mellitus or heart failure is present. Eplerenone was associated with a significant mortality benefit in this setting. Contraindications include serum creatinine higher than 2.5 mg/dL in men and higher than 2.0 mg/dL in women, as well as a potassium level higher than 5.0 mmol/L.[56]

Nitrates

Sublingual nitroglycerin should be administered to patients with ongoing ischemic chest discomfort. Nitrates can be used in the emergency department to assist with the diagnosis of coronary chest pain in patients with a nondiagnostic ECG, although relief of chest pain with sublingual nitroglycerin is not diagnostic of ACS. Intravenous nitroglycerin is useful in acute MI with recurrent ischemia, heart failure, or hypertension. Nitrates can be added to β-blockers or calcium channel blocker therapy for treatment of postinfarction angina. Clinical studies have failed to show a survival benefit for nitrates administered after infarction.[53,54] Nitrates should not be used in the presence of bradycardia, excessive tachycardia, hypotension, or right ventricular infarction.

Calcium Channel Blockers

The calcium channel blockers diltiazem and verapamil can be used to treat ongoing or recurrent ischemia, hypertension, or supraventricular tachycardia in

patients intolerant to β-blockers. These agents should not be used in the presence of heart failure, significant left ventricular dysfunction, or heart block. Long-term survival benefits have not been shown with this class of agents.[57] Diltiazem, verapamil, and amlodipine are useful in treating coronary artery spasm.

Statins

3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) are essential therapy in patients with ACS. Early administration is associated with a reduction in early adverse cardiovascular events, and therapy continued after discharge reduces the risk of recurrent infarction, death from coronary disease, stroke, and need for revascularization. High doses of potent statins should be initiated in the hospital (eg, atorvastatin 80 mg daily).[58]

Ranolazine

Ranolazine inhibits the late inward sodium current in myocytes and inhibits the deleterious effect of intracellular sodium and calcium seen during ischemia. In general, ranolazine is indicated for management of chronic angina and is not routinely used in ACS. However, in one trial, treatment was associated with a significant reduction in recurrent ischemia in women.[59]

HIGH-RISK COMPLICATIONS OF ACS

Heart Failure and Cardiogenic Shock

The presence of heart failure complicating ACS is associated with a significantly worse prognosis. Heart failure is often due to ischemia leading to hibernating or stunned myocardium, and improved left ventricular function can be restored by improving myocardial perfusion. Revascularization strategies are associated with improved survival, so an aggressive diagnostic and therapeutic management approach is indicated. Cardiogenic shock due to ACS can be present at hospital admission but often develops during the first 24 hours of hospitalization. Cardiogenic shock can occur following STEMI or NSTE-ACS. In patients younger than 75 years, emergency revascularization with PCI or coronary artery bypass graft was associated with improved survival at 6 months and 1 year in the SHOCK Trial ("SHould We Emergently Revascularize Occluded Coronaries for Cardiogenic ShocK"). Registry data also suggested benefits in well-selected patients older than 75 years. Intra-aortic balloon counterpulsation is

recommended in patients with persistent hypotension and shock, and mechanical circulatory assist devices can be used for refractory patients.[60-63]

Right Ventricular Infarction

Right ventricular infarction (RVI) can accompany acute inferior wall MI and lead to cardiogenic shock. It is estimated that 30% of inferior wall MIs are complicated by RVI, with shock in 10% to 15%. RVI causes acute right ventricular dysfunction and decreased right ventricular output, which leads to decreased left ventricular preload and decreased cardiac output. As the right ventricle dilates, the intraventricular septum may bulge into the left ventricle, further compromising left ventricular function. Findings on physical examination that suggest this condition are hypotension, clear lung fields, and elevated jugular venous pressure. Findings on ECG include ST-segment elevation in leads II, III, and aVF associated with ST elevation in lead V_1 and right-sided chest lead V_4R. These findings may be transient. Transthoracic echocardiogram shows a dilated, hypocontractile right ventricle and may show bulging of the septum into the left ventricle. Typical findings on catheterization of the right side of the heart include mean right atrial pressure greater than 10 mm Hg and right atrial pressure more than 80% of pulmonary artery occlusion pressure. Cardiac index is low.

RVI results from occlusion of the right coronary artery proximal to the origin of the right ventricular coronary artery branch. In the era before PCI for acute MI, in-hospital mortality from RVI was approximately 7%, less than the mortality rate for anterior MI but higher than that for inferior MI without RVI.[64] Survival has improved in the era of reperfusion therapy for acute MI.

Initial therapy for hypotensive patients with RVI is intravenous fluid challenge if jugular venous pressure is not elevated. Up to 1 L of intravenous saline should be infused, which may correct hypotension. Larger volumes may actually impair cardiac output by increasing right ventricular dilation at the expense of left ventricular filling. Inotropic medications and intra-aortic balloon counterpulsation are useful in patients who do not respond to fluid challenge. Intra-aortic balloon counterpulsation helps to decrease wall stress and increase coronary perfusion pressure. Maintenance of sinus rhythm and AV synchrony is also important.

Emergency revascularization of the occluded right coronary artery with PCI is now the cornerstone of therapy. After successful reperfusion, rapid recovery of

right ventricular function can be expected with low in-hospital mortality. If successful rapid reperfusion cannot be accomplished, marked hemodynamic impairment will persist for days, and in-hospital mortality is reported as high as 58%.[65] The majority of patients with RVI will have spontaneous recovery of right ventricular function, but this will occur slowly and may be incomplete.

Acute Severe Mitral Regurgitation

Acute severe mitral regurgitation, due to infarction and rupture of the head of a papillary muscle, is an uncommon complication of acute MI.[66,67] Acute severe mitral regurgitation is more likely to complicate inferior MI than anterior MI. Acute severe mitral regurgitation usually occurs within the first 24 hours of acute MI but may present on days 3 through 5. The diagnosis of acute severe mitral regurgitation should be suspected in patients with acute pulmonary edema complicating acute MI, especially inferior wall MI. The murmur of mitral regurgitation is often loud but at times is unimpressive due to high left atrial pressures and a low left ventricular–left atrial systolic gradient. Diagnosis is made by urgent echocardiography.

In patients with acute severe mitral regurgitation, early diagnosis and aggressive support with inotropic drugs, intra-aortic balloon counterpulsation, and vasodilators (if blood pressure allows) are vital in appropriately selected patients. Acute severe mitral regurgitation is associated with high in-hospital mortality. Urgent cardiac surgical repair is indicated as delays prior to surgery worsen survival. In the SHOCK Trial Registry, patients who underwent urgent mitral valve surgery had a 40% mortality rate, whereas patients who did not undergo surgery had a 71% mortality rate. The overall in-hospital mortality rate was 55%. Acute severe mitral regurgitation can occur due to papillary muscle rupture in the absence of extensive myocardial necrosis; therefore, repairing the mechanical valvular abnormality may confer long-term survival.

Postinfarction Ventricular Septal Rupture

Rupture of the interventricular septum is an uncommon complication of acute MI and leads to cardiogenic shock. This often occurs in the first 24 hours of infarction. This condition occurs in less than 1% of patients with STEMI. Ventricular septal rupture (VSR) may complicate either anterior or inferior wall STEMI. Patients will present with shock and pulmonary edema, and a loud holosystolic murmur is present on physical examination. Diagnosis is made by urgent Doppler echocardiography. Findings include right ventricular volume

overload, Doppler flow evidence of left-to-right shunting at the ventricular level, and visualization of septal rupture with color-flow Doppler. Right-heart catheterization shows higher oxygen saturations in the pulmonary artery than in the right atrium due to left-to-right shunting.

Urgent surgical repair of VSR is indicated. However, this condition is associated with a very high mortality rate even with surgical or medical therapy. Waiting several days before surgery to allow healing is not recommended because many patients will die during this waiting period. In the SHOCK Trial Registry, 31 of 55 patients with VSR underwent surgery, with a mortality of 81%. Only 4% of patients survived without surgery. Another series of 76 patients with VSR who underwent surgery reported a 30-day postoperative mortality of 49%.[68,69]

Left Ventricular Free Wall Rupture and Cardiac Tamponade

Left ventricular free wall rupture is an uncommon, lethal complication of acute MI. It is estimated to occur in 1% to 6% of patients with acute MI, although the true incidence is difficult to ascertain because the majority of patients will die immediately from electromechanical dissociation. The incidence of free wall rupture has likely decreased in the era of thrombolysis and primary PCI for acute MI. Patients at risk include older patients, those with a first MI, and women with anterior infarction. Short-term survival is possible if rupture is spontaneously sealed off by elevated intrapericardial pressure from hemopericardium.

These patients present with cardiogenic shock or after resuscitation from cardiac arrest. The diagnosis is made by emergency echocardiography, which shows a pericardial effusion of notable size, either loculated or diffuse, and may show the area of rupture.

In the SHOCK Trial Registry, 21 of 28 patients who were diagnosed with ventricular free wall rupture underwent surgery, with a 62% mortality rate. Six patients underwent pericardiocentesis only, and 3 survived. Other series describe operative mortality rates of 24% to 52%.[70,71]

Cardiac Arrest

It is estimated that 5% to 10% of patients with ACS will suffer sustained ventricular tachycardia or ventricular fibrillation during their hospitalization, usually in the first 48 hours. In some series, 4% to 11% of patients receiving emergency PCI for STEMI were resuscitated from out-of-hospital cardiac arrest.

Therapeutic hypothermia is now used widely after successful resuscitation in patients with significant neurological impairment. In STEMI patients resuscitated from cardiac arrest, it is recommended that hypothermia be initiated prior to or at the time of emergency coronary intervention. Indications for PCI to the culprit coronary stenosis are the same in this group of patients as in those with STEMI without cardiac arrest and resuscitation.[1,72,73]

SUMMARY

Acute coronary syndromes are classified as either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Rapid risk assessment and appropriate use of thrombolytic agents, PCI, surgery, and/or medical management are the keys to optimizing survival rates in these patients. High-risk complications, including cardiogenic shock, right ventricular infarction, acute severe mitral regurgitation, ventricular septal or wall rupture, and cardiac arrest, are uncommon but portend a significantly worse prognosis.

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CHAPTER 12

Arrhythmias and Related Devices

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Key words: supraventricular tachycardia, wide-complex tachycardia, reentry, bradycardia, sinus node dysfunction, atrioventricular block, pacemaker, implantable defibrillator

ARRHYTHMIAS

Pathophysiological Features of Cardiac Arrhythmias

The altered homeostatic environment present in critically ill patients is conducive to the generation of cardiac arrhythmias. Appropriate management of a dysrhythmia aims both to correct the rhythm disturbance itself and to identify and optimize predisposing conditions such as catecholamine excess or electrolyte disturbances. An understanding of the basic mechanisms of arrhythmia generation is also useful in selecting the optimal therapy.

Tachyarrhythmias

All 3 mechanisms of tachyarrhythmia are encountered in critically ill patients. *Reentrant arrhythmias* occur when different rates of myocardial conduction produce self-perpetuating loops of electrical activation. Electrical heterogeneity, such as that produced by myocardial scar, provides the substrate for reentry circuits. *Triggered arrhythmias* typically occur when myocardial repolarization is prolonged. Spontaneous after-depolarizations result in extra systoles, which can then trigger sustained arrhythmias in vulnerable myocardium. QT prolongation increases the vulnerable period in which triggered arrhythmias may occur. Finally, the ability of any myocardial cell to generate spontaneous depolarizations and generate a conducted electrical impulse is known as

enhanced automaticity. These 3 basic mechanisms are enhanced by hypoxia, catecholamine excess, electrolyte disturbances, toxins, and medications (eg, digoxin, antipsychotics, and antiarrhythmic agents), all of which are commonly encountered in critically ill patients.

Bradyarrhythmias

Bradyarrhythmias develop as a result of dysfunction in the conducting system of the heart, either from a failure of impulse generation at the level of the sinoatrial (SA) node or from a block at the level of the atrioventricular (AV) node or His-Purkinje system. Degeneration of the conducting system, as is frequently seen with aging, is the most common substrate for bradyarrhythmias. Hypoxia, myocardial ischemia, metabolic derangements, and medication effects may increase the risk of bradycardia. Increases in vagal tone can occur with pain, coughing, and nausea and may cause significant bradycardia even in individuals with normal conducting systems.

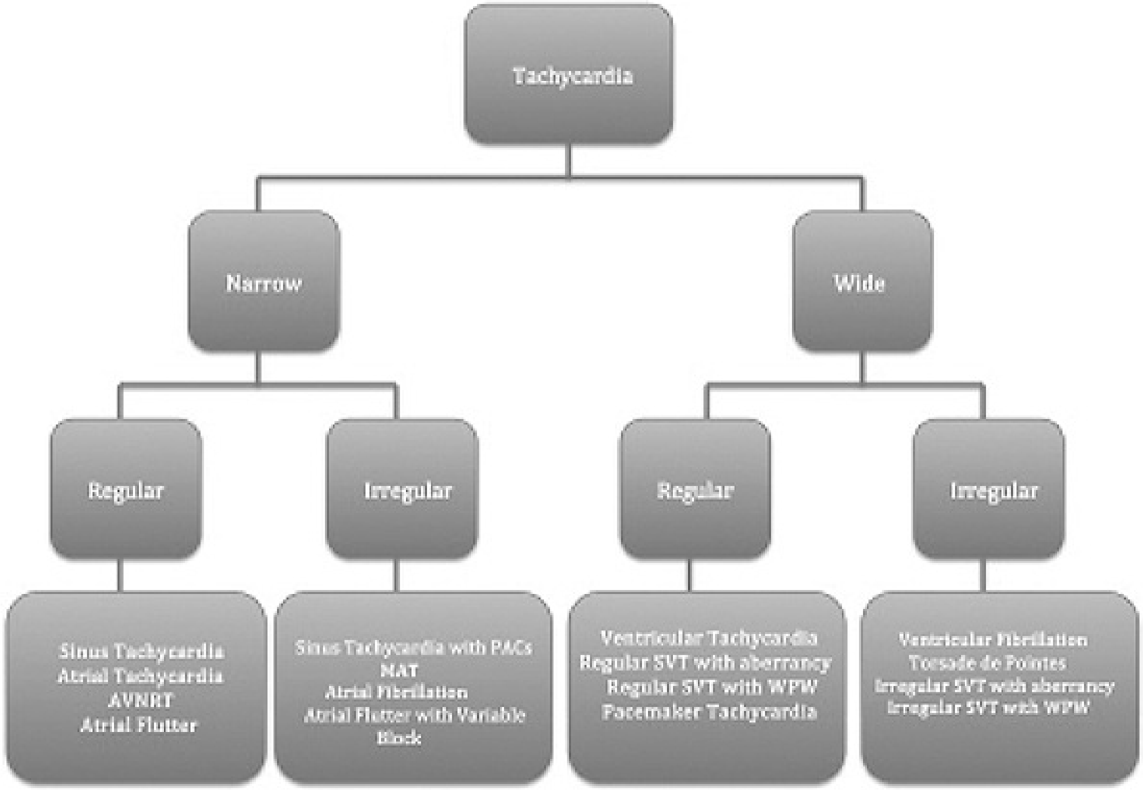
General Approach to Arrhythmia Diagnosis and Management

Management of any cardiac arrhythmia should be dictated initially by the patient's clinical condition. Hemodynamically unstable arrhythmias resulting in shock should be managed by prompt electrical cardioversion or defibrillation according to the appropriate advanced cardiac life support (ACLS) algorithm. Efforts to restore hemodynamic stability should also include general resuscitation methods such as airway management and fluid administration.

While a rhythm strip will direct initial management, a 12-lead electrocardiograph (ECG) is frequently required to identify the offending arrhythmia as well as help diagnose any underlying precipitants such as coronary ischemia or electrolyte abnormalities.

The diagnosis of any arrhythmia hinges on a description of the rate, morphological features, and regularity of the atrial activity; the rate and width of the subsequent ventricular QRS complex; and the relationship of the latter to the atrial activity (**Figure 1**).

Figure 1. Differential diagnosis for tachycardia classified by QRS width and regularity



Abbreviations: AVNRT, atrioventricular nodal reentrant tachycardia; SVT, supraventricular tachycardia; WPW, Wolf-Parkinson-White syndrome.

The rate can be classified as bradycardic (<60 beats per minute [bpm]), tachycardic (≥100 bpm), or normal (60-99 bpm). The atrial and ventricular rates may not be the same, particularly in cases of AV dissociation. Sinus P waves are generally upright in the inferior leads (II, III, aVF). Different P-wave morphological features and axes suggest ectopic atrial pacemakers. An irregular rhythm is typically supraventricular in origin. A wide QRS (>120 milliseconds) is usually indicative of a ventricular focus, particularly in patients with underlying heart disease, but may result from aberrant conduction due to a preexisting bundle branch block (BBB) or rate-dependent BBB or, more rarely, from conduction via an accessory pathway.

Supraventricular Tachyarrhythmias

Sinus Tachycardia

Sinus tachycardia is a normal response to physiological stress, and treatment is directed at the underlying cause. Sinus tachycardia is characterized by regular, monomorphic P waves that are upright in the inferior leads and present before

every QRS complex; sinus tachycardia displays heart rate variability over time with rates typically not exceeding 220 bpm minus the patient's age in years (**Figures 2** and **3**).

Figure 2. Electrocardiographic findings of regular, narrow tachyarrhythmias

Figure 3. Electrocardiographic findings of irregular, narrow tachyarrhythmias

Paroxysmal Supraventricular Tachycardia

Paroxysmal supraventricular tachycardia (PSVT) refers to a category of arrhythmias that occur at rates from 150 to 250 per minute. They frequently terminate spontaneously, hence the term *paroxysmal*.

AV nodal reentrant tachycardia (AVNRT) is the most common form of PSVT, with the reentry circuit completely contained within the posterior right atrium near the AV node.

In AV reentrant tachycardia (AVRT), an accessory pathway provides one of the reentry limbs. Antegrade conduction to the ventricles typically occurs through the AV nodal limb and retrograde conduction occurs via the accessory pathway. This is known as orthodromic conduction. The reverse, or antidromic conduction, produces ventricular preexcitation characteristic of the Wolf-Parkinson-White syndrome and results in a wide-complex tachycardia (WCT).

Most people who display ventricular preexcitation will have normalization of their QRS complex when they develop orthodromic AVRT. Given the involvement of the AV node, AVNRT and AVRT are often very sensitive to vagal maneuvers and will terminate with adenosine in 90% of cases. Calcium channel blockers produce more sustained AV nodal blockade and are useful second-line agents in orthodromically conducted paroxysmal atrial tachycardia.

Atrial tachycardia (AT) is a focal arrhythmia with a P wave that is morphologically distinct from baseline. The form of the P wave varies according to the anatomical focus of the AT. Heart rates can range from 120 to 250 bpm. AT frequently displays less heart rate variability than sinus tachycardia and often demonstrates a “warm-up” and “cool-down” in rate during initiation and termination. AT is less common in ICU patients but may occur in patients with conditions predisposing to atrial stretch. The response to treatment is variable depending on the underlying mechanism producing the AT. AT caused by micro-reentry within the atrium will respond well to adenosine or direct-current (DC) cardioversion. AT related to triggered activity or increased automaticity will usually respond to AV nodal blockade or antiarrhythmic agents such as sotalol or amiodarone. Catheter ablation is an option for refractory cases.

Multifocal Atrial Tachycardia

Multifocal AT (MAT) is characterized by increased automaticity producing multiple foci of atrial activity, each producing a morphologically distinct P wave with variable PP and PR intervals and an irregularly irregular ventricular response. MAT is classically associated with severe chronic lung disease and is generally refractory to rhythm control. Treatment of the underlying cause is the most effective therapy. Alternatively, a rate control strategy with calcium channel blockade is usually effective. β-Blockers are also useful, but must be used cautiously given the risk of increasing airflow obstruction.

Atrial Flutter and Fibrillation

Atrial flutter and atrial fibrillation (AF) represent a continuum of disease and often coexist. Macro-reentry circuits, most often in the right atrium, produce rapid atrial contractions at rates of 250 to 300 bpm. Typical atrial flutter activates the right atrium in a counterclockwise fashion, causing flutter waves that are inverted in the inferior leads and produce a “saw-tooth” pattern. AV conduction typically blocks conduction in a discrete fraction of the atrial rate, typically 2:1 for a rate of 150 bpm producing a regular tachycardia, although variable block

may also occur, producing an irregular rhythm.

Multiple foci of increased atrial automaticity and small reentry circuits combine to produce AF. Atrial activity is disorganized, and no distinct P wave is present on the ECG. Transmission of fibrillatory waves through the AV node is inconsistent, producing a characteristically irregularly irregular ventricular response up to 180 bpm depending on the AV nodal conduction. AF is the most common sustained arrhythmia and can occur in the absence of obvious structural heart disease ("lone AF"). More commonly, AF is associated with diseases that cause dilatation of the atria, such as hypertension, heart failure, and chronic obstructive pulmonary disease, or AF occurs with aging of the electrical conducting system as part of the tachy-brady syndrome. AF also commonly occurs in states of high adrenergic tone, such as following surgery.

Treatment should be individualized. Limited data are available to guide management of AF in hospitalized patients, so most recommendations are extrapolated from ambulatory patients. Hemodynamically unstable patients should receive synchronized DC cardioversion. Stable patients are appropriate candidates for a trial of medical therapy either by chemical cardioversion (rhythm control) or control of the ventricular response rate. Given that studies show no difference in long-term mortality, rate control is often the preferred initial treatment in asymptomatic patients, using either β-blockers or calcium channel blockers. Digoxin remains an option for rate control, particularly in the face of a marginal blood pressure. Rate control to the range of 90 to 110 bpm should be sufficient to improve hemodynamics, as stricter rate control may compromise cardiac output. The restoration of atrial contraction may also increase cardiac output, particularly in those with limited hemodynamic reserve. IV amiodarone is the preferred agent given its effectiveness and hemodynamic stability. Once sinus rhythm is restored, a patient may be transitioned to oral amiodarone therapy to help maintain sinus rhythm. While other antiarrhythmic agents are available to restore and maintain sinus rhythm, their risk of causing proarrhythmia limits their use in critically ill patients.

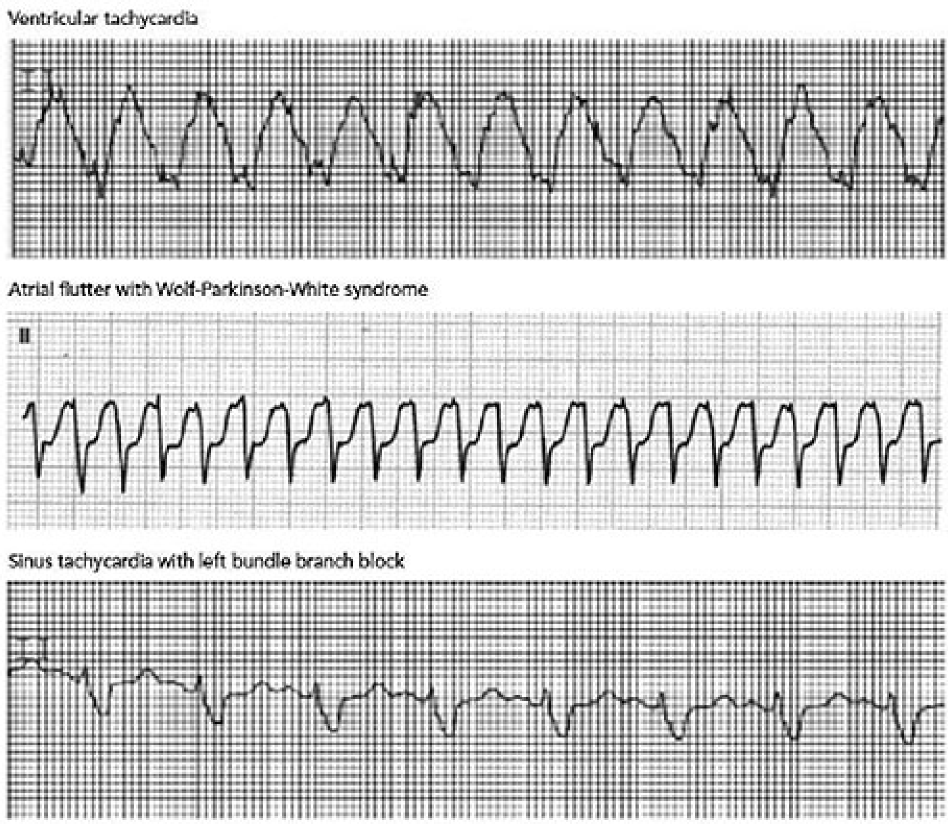
Ineffective atrial emptying leads to blood stasis and clot formation, predominantly within the left atrial appendage. This carries a long-term risk of embolic stroke as well as more acute embolization following cardioversion, if the patient remains in AF for more than 48 hours. The actual daily risk of stroke from AF is quite small, and the benefits of anticoagulation need to be balanced against the increased risk of bleeding in critically ill patients. The first-line anticoagulant in the ICU is IV heparin, because it has a short half-life and can be

reversed effectively with protamine. Once a decision is made to maintain anticoagulation long-term, the patient should be switched to a longer acting agent, such as one of the novel oral anticoagulants or warfarin.

Wide-Complex Tachycardia

The term *WCT* (**Figure 4**) stems from the fact that supraventricular tachycardia (SVT) with aberrancy can be difficult to distinguish from ventricular tachycardia (VT). While a number of diagnostic criteria exist, none are completely reliable. Thus, when doubt exists as to the exact diagnosis, it is safest to presume VT and treat as such given the higher mortality with VT.

Figure 4. Electrocardiographic findings of regular, wide tachyarrhythmias



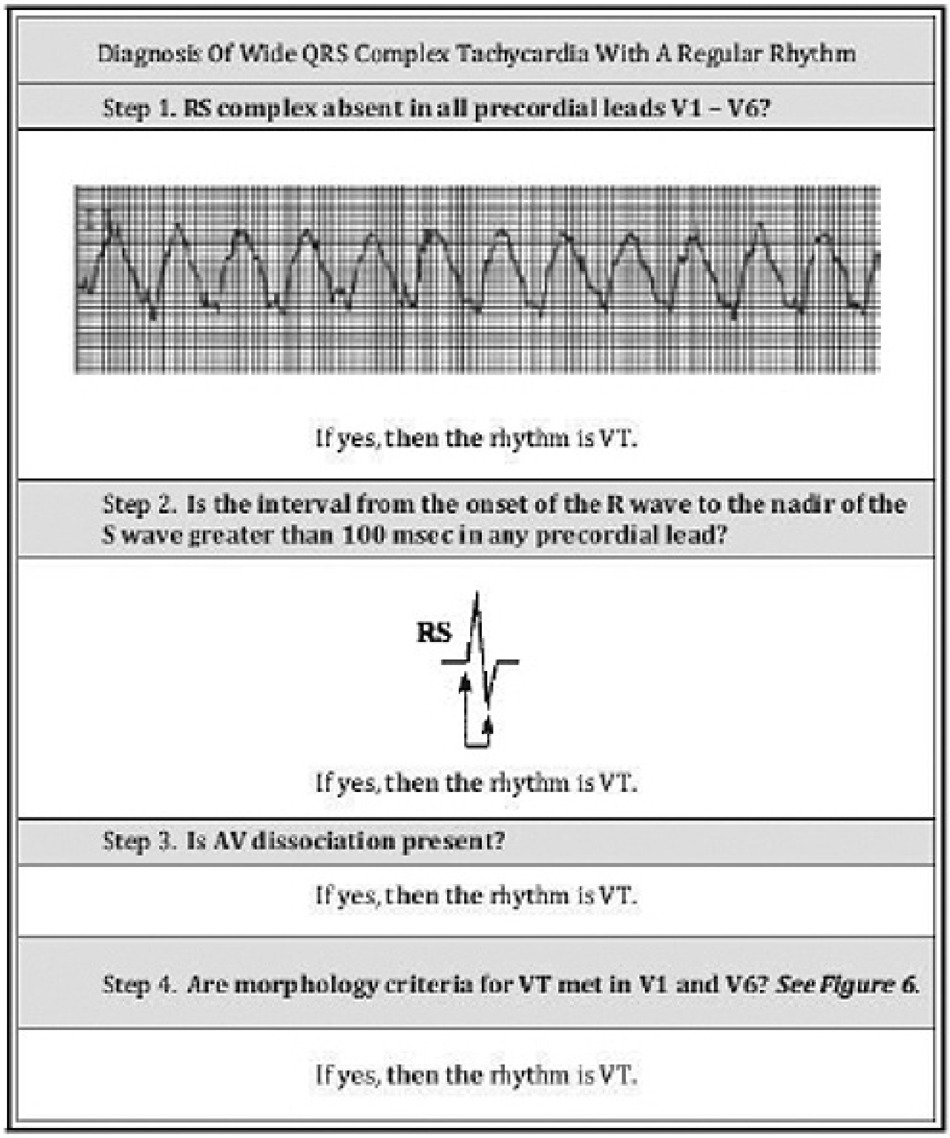
Ventricular Tachycardia

VT is the most common form of WCT, particularly in the presence of underlying heart disease. Indeed, the electrical heterogeneity produced by myocardial scar or ischemia provides the substrate for the development of reentry circuits, which account for the majority of VT cases. VT also may arise as a triggered arrhythmia or from increased automaticity. VT may present as either a regular

VT (monomorphic VT) or irregular VT (polymorphic VT). The clinical presentation of VT ranges from hemodynamically stable palpitations to sudden cardiac death. Underlying cardiac function is an important predictor of outcome; more hemodynamically significant VT is likely to occur in patients with more severe degrees of ventricular dysfunction. Idiopathic monomorphic VT, occurring in the absence of underlying heart disease, generally has a more favorable prognosis.

As a general rule, the more unusual the appearance of the ECG, the more likely the diagnosis is VT rather than SVT with aberrancy. AV dissociation is highly specific for VT, but P waves may be difficult to identify with tachycardia. Wider QRS duration, particularly when it exceeds 160 milliseconds, is highly indicative of VT, but VT originating close to the intraventricular conduction system may have a width of less than 140 milliseconds. Precordial concordance of the QRS complex is generally indicative of VT but can be seen rarely in SVT conducted over a posterior accessory pathway. An RS interval of less than 100 milliseconds in one or more precordial leads points to VT but also can be seen in SVT in a patient receiving antiarrhythmic agents or a patient with a preexisting left BBB and some form of preexcitation. Diagnostic algorithms, such as the Brugada criteria (**Figure 5**), may differentiate VT from aberrant SVT, but their predictive value is not absolute. An examination of the baseline ECG is often necessary to establish whether a baseline BBB or preexcitation pattern existed and whether the morphological state of the BBB has changed.

Figure 5. Brugada algorithm for diagnosis of wide QRS complex tachycardia



Information taken from Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation*. 1991;83:1649-1659.

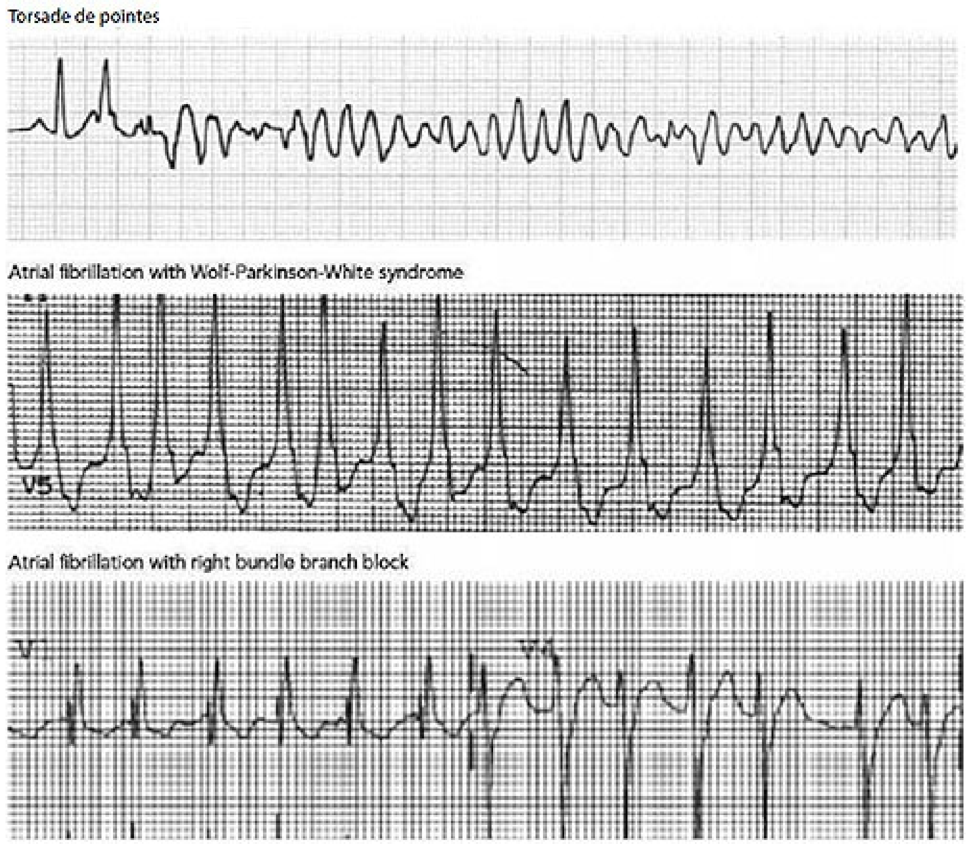
Treatment of VT is dictated by clinical stability. VT is often hemodynamically unstable with a high risk of degenerating into pulseless VT or ventricular fibrillation (VF). Unstable or deteriorating patients should receive prompt, synchronized DC cardioversion. Patients with pulseless VT or VF should be defibrillated immediately. Hemodynamically stable patients with monomorphic VT may be suitable for a trial of chemical cardioversion with IV amiodarone. IV lidocaine may be considered as a second-line adjunct for a patient with recurrent VT. Adenosine should be avoided in patients with WCT unless it is clear that it represents SVT with a preexisting BBB. AF with antegrade conduction along an accessory pathway, as seen in the Wolf-Parkinson-White syndrome, is an

uncommon cause of WCT. Antidromic conduction of AF over an accessory AV pathway without the refractoriness of the AV node allowing the development of tachycardia with very high heart rates and can degenerate into VF. As such, the treatment of preexcited AF resembles that of VT. AV nodal blocking agents are contraindicated as they may accelerate conduction along the accessory pathway. DC cardioversion is mandated for hemodynamically unstable Wolf-Parkinson-White syndrome.

Polymorphic Ventricular Tachycardia

Polymorphic VT is an irregular WCT that is usually unstable and requires immediate defibrillation (**Figure 6**). Polymorphic VT occurs in the context of structural heart disease, in particular cardiac ischemia or reperfusion, or in rarer idiopathic conditions such as catecholaminergic polymorphic VT. Torsade de pointes (TdP) is a specific form of polymorphic VT that is associated with congenital or acquired prolongation of repolarization and is characterized by QT prolongation, which can trigger arrhythmias due to after-depolarizations. TdP is pause dependent and is characterized by a cyclical reversal of the QRS axis in a twisting pattern. The recognition of TdP is essential because first-line therapy is magnesium. Any medications capable of prolonging the QT interval should be stopped, such as antipsychotic and antiarrhythmic agents. Hypokalemia and hypomagnesemia should be corrected. In refractory cases, overdrive pacing can be attempted.

Figure 6. Electrocardiographic findings of irregular, wide tachyarrhythmias



Bradyarrhythmias

Bradyarrhythmias can result from failure of impulse generation from the SA node or failure of transmission along any part of the conducting system. Such disturbances can arise from either structural degeneration of the conducting system, frequently seen with aging, or factors including hypoxia, medication effects, electrolyte disturbances, and myocardial ischemia. Extrinsic causes are common in the ICU, and their correction is often sufficient to prevent further bradycardia.

Treatment of bradycardia depends largely on the clinical presentation. Consideration also should be given to the type of rhythm observed, as some types are prone to progression to a more hemodynamically unstable rhythm and warrant closer observation.

Disorders of Impulse Generation

These disorders are related to impaired impulse generation by the SA node. SA node dysfunction is the result of decreased automaticity and is typically seen as part of the sick sinus syndrome in elderly patients, although increased vagal

tone, as seen with nausea and pain, and medication effects are also common in the ICU.

Sinus Bradycardia, Exit Block, and Arrest

Sinus bradycardia, defined as a heart rate less than 60 bpm, may occur as a result of sick sinus syndrome but is frequently physiologically driven by hypoxemia, increased intracranial pressure, hypothermia, electrolyte derangements, medication effects, myocardial ischemia, or infarction. Treatment starts with correction of the causative condition. Drug intoxications producing sinus bradycardia may require specific antidotes. Additional treatment aimed specifically at accelerating the heart rate, such as catecholamine infusions or pacing, may be indicated if the patient is hemodynamically unstable.

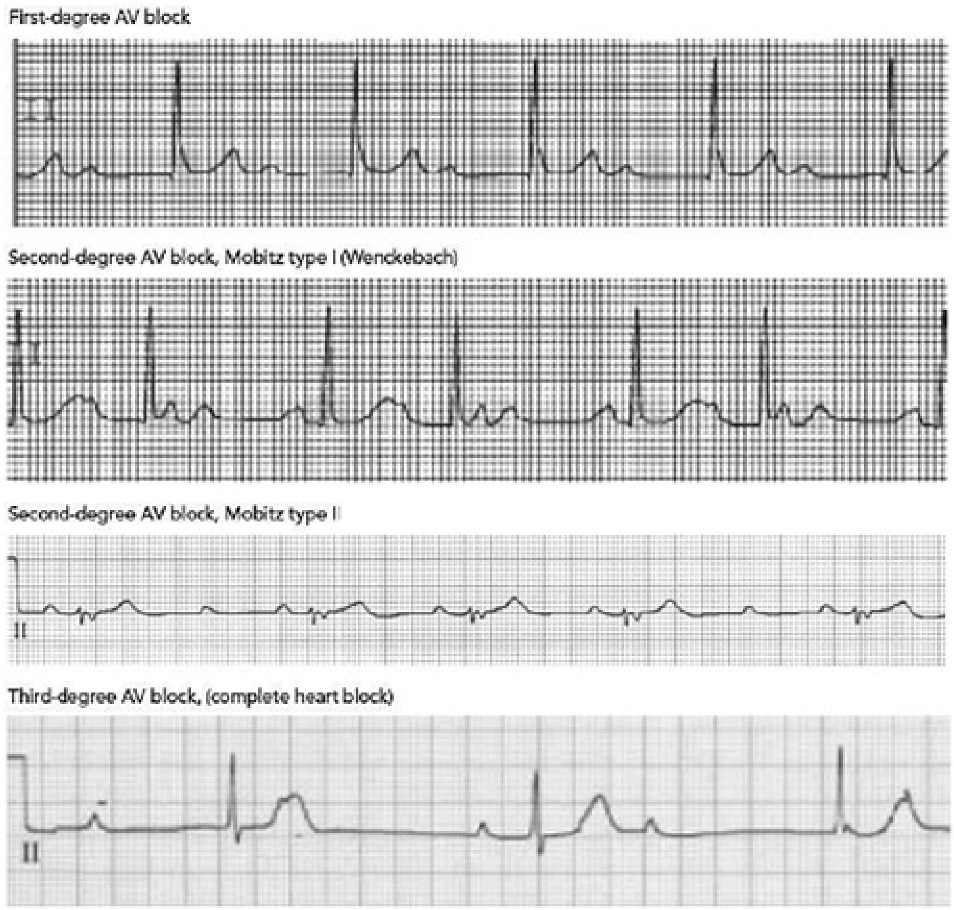
Sinus exit block is due to a failure of the SA node impulse to propagate into the adjacent atria myocardium. It appears as dropped P waves on the surface ECG. Sinus arrest occurs when SA node automaticity is depressed. The resulting sinus pause may last several seconds, followed by eventual resumption of activity or development of an escape rhythm that may or may not be hemodynamically stable. Both may be caused by ischemia, cardiac inflammation, antiarrhythmic therapy, or high vagal tone. Pacing is indicated to manage symptomatic pauses.

Impulse Conduction Disturbances

Atrioventricular Block

Pathological prolongation of AV node conduction may occur due to high vagal tone, AV nodal blocking medications, myocardial ischemia or infarction, infiltrative diseases, and age-related sclerosis of the conducting system and can occur following cardiac surgery, particularly valve replacements (**Figure 7**).

Figure 7. Electrocardiographic findings associated with atrioventricular (AV) block



Slowed conduction through the AV node produces a prolonged PR interval on the ECG in first-degree AV block. Intrinsic nodal disease, ischemia, medications, and increased vagal tone all can cause first-degree AV block. First-degree AV block generally does not require treatment; however, pacing may be indicated with a PR interval greater than 300 milliseconds if there is evidence of inadequate cardiac output from impaired atrial filling.

In second-degree AV block, some of the atrial impulses are no longer being transmitted to the ventricles, and 2 characteristic patterns are observed. Mobitz type I, also known as Wenckebach, entails progressive prolongation of the PR interval until a P wave is dropped. This produces a regularly irregular rhythm and the QRS complex is typically narrow, as the block is usually in the AV node. Mobitz I is usually asymptomatic and the treatment is directed at finding the precipitant, the list of which is identical to that seen for first-degree AV block. Short-term progression to complete heart block (CHB) is rare, and pacing is required only if a higher heart rate is necessary to maintain an adequate cardiac output, as may be seen in individuals with poor ventricular function.

Mobitz II entails failure of conduction without progressive PR prolongation. The block is frequently lower in the conducting system at the level of the His-Purkinje fibers, and there is a greater likelihood of hemodynamic instability and progression to CHB. In Mobitz II, the ratio of nonconducted to conducted P waves may be constant or variable. Of note, Mobitz I and Mobitz with 2:1 block cannot be reliably distinguished on surface ECG, although a wider QRS is suggestive of Mobitz II. Initial treatment consists of identifying and correcting the underlying causes. Temporary pacing may be required in symptomatic patients, and elective permanent pacing may be considered because the risk of progression to CHB is high. Atropine is usually ineffective as the block is usually below the AV node; paradoxically, atropine may worsen the block by accelerating the atrial rate faster than the His-Purkinje system is able to repolarize.

Third-degree heart block, also known as complete heart block (CHB), involves complete dissociation between the atrial and ventricular rates. The hemodynamic stability is dependent on the rate and location of the resultant escape rhythm and the underlying myocardial function. A narrow QRS escape rhythm originating within the AV node is likely to be faster and more stable than a wider one originating in the His bundle or below. CHB is less likely to be reversible, and the majority of patients require permanent pacing. While permanent pacing is being arranged, patients can be managed with either temporary pacing or catecholamine infusions such as dopamine or epinephrine to accelerate the escape rhythm. Although transcutaneous pacing can be rapidly deployed, it is uncomfortable for the patient and capture may be intermittent. Thus, transcutaneous pacing generally should be followed by placement of a temporary transvenous pacemaker.

Escape Rhythms

In sinus arrest and high-grade AV block, impulses from the SA node or atria are absent or blocked, producing pauses longer than the sinus cycle. This allows the AV node to become the dominant pacemaker and produce a junctional escape rhythm. A junctional escape rhythm is identified on ECG by regular, narrow QRS complexes without preceding P waves, although inverted retrograde P waves can sometimes be found buried within the QRS. AV nodal or bundle of His escape rates typically vary between 40 and 60 bpm. A junctional escape rhythm is usually hemodynamically stable and typically does not require pacing.

When both the SA and AV nodes fail to generate or conduct supraventricular

impulses, a ventricular pacemaker can provide an escape rhythm. Ventricular escape rhythms are regular with rates less than 40 bpm. AV dissociation secondary to high-grade AV block differs from VT, because the atrial rate in VT exceeds the ventricular rate in AV block. Lidocaine is contraindicated in the presence of a ventricular escape rhythm because this agent can abolish the escape rhythm and cause asystole. Ventricular escape rhythms can be unstable and usually require temporary or permanent pacing.

Accelerated idioventricular rhythm (AIVR) is a ventricular rhythm originating from the bundle of His or ventricular myocytes. AIVR is characterized by a wide complex at a rate between 60 and 100 bpm. Therefore, AIVR is faster than a ventricular escape rhythm but slower than VT. This rhythm is classically observed during reperfusion following acute myocardial infarction but also can result from electrolyte abnormalities or drug intoxication, including cocaine and digoxin.

AIVR represents either an accelerated escape rhythm in the presence of AV dissociation during CHB or an ectopic ventricular focus with enhanced automaticity functioning as a dominant pacemaker by firing at a rate greater than the sinus node. AIVRs can be found in patients without structural heart disease but are most commonly found in patients with coronary artery disease. Although AIVR previously was considered a benign rhythm, it is associated with increased mortality when observed during return of spontaneous circulation following cardiac arrest. In addition, AIVR previously was considered a marker of successful reperfusion, but recent data suggest that AIVR is a marker of delayed reperfusion and larger infarct size in patients with ST-segment elevation myocardial infarction.

Cardiac Implantable Electronic Devices

Comprehensive critical care management requires basic knowledge of cardiac device function, device indications, perioperative management, and common complications. Cardiac implantable electronic devices (CIEDs), such as pacemakers and defibrillators, may provide atrial, ventricular, and biventricular functions. In addition to traditional transvenous and epicardial systems, subcutaneous intracardiac cardioverter defibrillators (ICDs) and leadless pacemakers are now available. Furthermore, many devices are considered “magnetic resonance conditional,” and an increasing population of patients have implantable loop recorders for extended monitoring of arrhythmias and syncope.

Indications and Device Selection

Pacemakers are indicated for symptomatic bradyarrhythmias, most commonly sinus node dysfunction or AV block. An increasing number of patients warrant biventricular pacing for the treatment of chronic systolic heart failure in the setting of left BBB. ICDs are indicated for primary or secondary prevention of sudden cardiac death due to VT and fibrillation.

Decisions regarding single- versus dual-chamber devices depend on the estimated longevity of AV conduction and the presence of chronic atrial arrhythmias. Single-chamber atrial devices are less common in the United States, likely reflecting concern for subsequent AV block. Dual-chamber pacing reduces successive AF and may improve a patient’s quality of life and functional status. Right ventricular apical pacing has an increased risk for congestive heart failure and therefore should be minimized with programming algorithms and consideration for nonapical lead placement and biventricular leads for chronic pacing. Dual-chamber defibrillators provide additional support for diagnosing and distinguishing between supraventricular rhythms in appropriate patient populations as well as atrial-based pacing support for sinus node dysfunction.

Modes and Programming

Device nomenclature is abbreviated with 5 letters corresponding to the locations of pacing, sensing, response to sensing, rate responsiveness, and multisite pacing (**Table 1**). Rate responsiveness alters the paced rate according to changes in bodily metabolic requirements. Typically, this is accomplished with accelerometer data, usually blended with additional data such as oxygen saturation, QT interval, respiratory rate, temperature, minute ventilation, endocardial acceleration, or changes in right ventricular impedance during the cardiac cycle.

Table 1. Standard Pacemaker Nomenclature

Position I	Position II	Position III	Position IV	Position V
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	T = triggered	R = rate modulation	A = atrium
V = ventricle	V = ventricle	I = inhibited		V = ventricle
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A +

Basic device functions are programmed at the time of insertion or at the time of device interrogation. These include parameters for minimum rate, maximum atrial tracking rate, AV delay, blanking periods, refractory periods, mode switching, defibrillator zones, and discriminators for SVT.

Mode switching allows a device to automatically change from a triggered to a nontriggered mode, for instance DDD to DDI, if the prespecified criteria are met. This feature, along with the preprogrammed maximum tracking rate, limits the tracking of rapid ventricular response to an atrial tachyarrhythmia.

Refractory and blanking periods are programmed to minimize oversensing. After a stimulated electrical impulse, the amplifier turns off for the assigned blanking period. Subsequently, the refractory period allows for sensed intrinsic activity prior to completion of triggered paced activity. If an impulse is sensed during the refractory period, the subsequent paced beat will be inhibited. During pacemaker-mediated tachycardia, an endless loop is maintained from a sensed retrograde atrial signal followed by a ventricular paced beat. To prevent further episodes, adjustments may be required in the post–atrial refractory period.

ICD therapy is programmed in multiple zones based on detection of VT or VF. Detection is based primarily on rate and duration but may include more advanced discriminators to identify SVT, including onset, regularity, and morphological features. Often, therapy zones are programmed in a tiered manner to allow for increasing support with antitachycardia pacing and increasing output of high-energy shocks with repeated therapy. Antitachycardia pacing provides painless electrical stimulation at a shorter interval than the arrhythmia in order to interrupt a reentry circuit of monomorphic VT.

The response of a CIED to magnet application varies by the type of device. In general, pacemakers switch to an asynchronous mode and defibrillators inhibit tachyarrhythmia therapy without changing the pacing mode. The rate of asynchronous pacing is based on the device manufacturer. Rarely, devices can be programmed with magnet therapy off, and there would be no response to magnet application.

Analysis of Device Function

When device function is in question, an ECG, chest radiograph, and

interrogation of the device should be performed. A cardiologist with device experience and potentially a device company representative should be contacted to assist with interrogation and troubleshooting. A chest radiograph can assist with identification of the device type, number and location of leads, and in some cases identification of the device manufacturer.

ECGs and telemetry should be evaluated for common device problems, including loss of capture, undersensing, and oversensing. Intracardiac electrograms, local signals from intracardiac electrodes, show what the device is detecting. Intracardiac electrograms can provide real-time information or stored data after an event. The origination of the intracardiac electrograms is noted by marker channels, and several annotations help identify events such as sensed beats, pacing, and tachycardia therapy.

When a pacing artifact is visualized but not followed by an appropriate electrical stimulus, loss of capture is present. Loss of capture can be a result of programming, changes in the lead or myocardium interface, lead movement or dislodgement, or lead fracture. A problem involving the lead interface with the pulse generator header may cause failure to output with no pacing artifact.

Undersensing results when an appropriate electrical signal is not sensed. Common causes include signal amplitude below sensing threshold or timing during the blanking period. Undersensing may result in inappropriate or asynchronous pacing. In an ICD, atrial undersensing can result in inability to diagnose atrial arrhythmia, interfere with SVT algorithms, and result in inappropriate detection of VT. In an ICD, ventricular undersensing can result in failure to detect and treat VT or VF. When undersensing is identified, adjustments to the lead sensitivity and blanking or refractory periods may be necessary.

Oversensing is the result of faulty sensing of either a nonphysiological or physiological signal. Nonphysiological signals include electromagnetic interference or mechanical problems with the sensing circuit. Physiological signals include inappropriately sensed signals, most commonly T waves or far-field electrograms, or extracardiac myopotentials including diaphragmatic and pectoral signals. Atrial oversensing may result in failure to pace the atrium, inappropriate tracking and ventricular pacing, or unnecessary mode switching. In a pacemaker, ventricular oversensing may result in failure to pace the ventricle and, importantly, can result in inappropriate detection and treatment for VT or VF in ICDs. Several device algorithms are available to assist with oversensing

and may need further adjustment based on individual patient characteristics, risk of arrhythmia, and source of inappropriate signals. The main goal is to reduce oversensing while continuing to safely monitor for ventricular arrhythmias.

Perioperative Management

Perioperative management of a CIED should be performed in a systematic fashion with an integrated team approach. Preoperatively, pacemaker dependency, baseline interrogation, battery status, and possible complicating factors should be identified. Data typically can be obtained from recent Device Clinic visit information, but if this is not available, these factors should be addressed prior to procedures. Electromagnetic interference from electrocautery in proximity to the device may interfere with various device functions transiently or, much less often, permanently. Potential complications include oversensing, triggering of rate responsiveness, device programming reset, pulse generator malfunction, and lead myocardial interface reactions. In high-risk settings, reprogramming to asynchronous mode and/or disabling tachycardia therapy is recommended. It is imperative that patients with changes to device settings be flagged for reprogramming postprocedurally. We recommend both wristband application and electronic medical chart documentation.

SUMMARY

Accurate diagnosis and management of cardiac arrhythmias require attention first to a patient's clinical status. Hemodynamically unstable tachyarrhythmias should be corrected electrically with either DC cardioversion or defibrillation as appropriate. Careful and systematic examination of all available ECG data, including 12-lead tracings of the arrhythmia, after correction and comparison with the patient's baseline ECG may be necessary to make the correct diagnosis. A similar approach is taken with bradyarrhythmias; hemodynamically unstable rhythms require either immediate pacing or infusion of chronotropic agents. It is imperative to systematically seek out the factors precipitating the arrhythmia, as these are commonly found in ICU patients. A working knowledge of device-related therapy is important, as the number of ICU patients with these devices continues to increase.

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CHAPTER 13

Valvular Heart Disease, Acute Aortic Dissection, and Patient Care After Cardiac Surgery

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Key words: valvular heart disease, aortic dissection, cardiopulmonary bypass, cardiac tamponade post cardiac surgery

VALVULAR HEART DISEASE

Valvular heart disease is becoming more common as our population ages. This section briefly covers the pathophysiological characteristics of aortic and mitral valve disease. Readers are referred to the 2014 update of the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients With Valvular Heart Disease for a recent, comprehensive review of this area of cardiovascular medicine, surgery, and transcatheter interventions.

Aortic Stenosis

Aortic stenosis (AS) is the most common valvular disease in the United States. A bicuspid aortic valve is present in approximately 1% to 2% of the population; this congenital defect is prone to early calcification and stenosis. Calcific AS appears to be an inflammatory disease, much like atherosclerosis, and shares several features with coronary artery disease, including the propensity to affect men, older persons, and people with hyperlipidemia. In calcific AS, the valve leaflets become progressively calcified, limiting valve motion and area. Rarely, rheumatic aortic disease is seen with concomitant mitral valve involvement. The pathological process differs in that the commissures become fused in rheumatic disease, which is not seen in calcific AS.

AS has an insidious onset, but the onset of symptoms marks the beginning of a large decline in function. Often because of aging, the aortic valve will calcify and stenose, causing a fixed obstruction to flow. Normally, symptoms do not present until well into the seventh and eighth decade of life, although accelerated disease is not unheard of. Symptoms include angina, syncope, and overt failure and signify end-stage disease. Following the onset of symptoms, 5-year survival rapidly drops to zero. Current class I recommendations by the ACC/AHA guidelines for valve replacement include the following:

1. Symptomatic patients with severe AS
2. Patients with severe AS undergoing other cardiac surgery
3. Patients with severe AS and an ejection fraction less than 0.5

The reader is referred to the ACC/AHA guidelines for a thorough discussion of class II indications.

All valvular disease affects left ventricular (LV) volume and pressure parameters, and AS is no exception. With the fixed outflow obstruction of a steadily shrinking orifice, the LV must generate more force to maintain cardiac output. Because of the chronicity of the disease, the LV adapts by increasing its wall mass and maintaining normal LV volume. The increased wall thickness is usually able to balance the increased interventricular pressure caused by the stenotic valve, maintaining a normal ejection fraction. These patients have high valve gradients reported via echocardiography. When the LV does not have the appropriate wall thickness to combat the increased wall stress, such as when the LV becomes dilated, then ejection fraction will decrease, and valve gradients may appear to normalize. Knowing how the stenotic valve has affected the ventricle will assist in appropriate hemodynamic management.

Patients with AS rely heavily on heart rate for maintenance of cardiac output. Diastolic filling is slowed by the hypertrophied, noncompliant LV. Tachycardia reduces diastolic time significantly, effectively reducing LV preload, stroke volume, and cardiac output. Normal sinus rhythm is also important because the hypertrophied LV is unable to fill normally without an atrial contraction. Hypovolemia and systemic hypotension are poorly tolerated in these patients. The thickened myocardium requires more time for coronary perfusion, and shortened diastolic times and low coronary perfusion pressures set the stage for ischemia.

Mitral Stenosis

Mitral stenosis (MS) is almost always a complication of previous rheumatic fever. Onset of symptoms is usually gradual. As the valve orifice shrinks, the left atrium (LA) dilates to accommodate the increased volume. Increased volume leads to the increased pressure that is needed for LV filling. This leads to stasis of blood flow and the predisposition to form thrombi as well as a high incidence of supraventricular tachycardia, especially atrial fibrillation. Lack of effective atrial contraction further reduces LV preload and is generally poorly tolerated, given the decrease in cardiac output.

With time, the increased LA pressure is transmitted backward to the pulmonary capillaries. Acute increases in LA pressure can lead to pulmonary edema. Eventually, the increased capillary pressure will lead to elevated pulmonary vascular resistance (PVR) and irreversible pulmonary hypertension. Acute increases in PVR can precipitate overt right-sided heart failure.

Management of the patient with MS is focused on maintaining normal sinus rhythm, avoiding tachycardia, and maintaining an even fluid balance. Aggressive volume loading can lead to pulmonary edema in patients with severe disease; use of invasive monitoring (intra-arterial blood pressure monitoring, pulmonary artery catheter) can assist in fluid and blood pressure management in patients who will experience large fluid shifts. Acute elevations in PVR, such as those caused by hypoxia, hypercarbia, and acidosis, must be avoided. Medical therapy is usually ineffective in these patients, because MS is a mechanical obstruction to flow. Class I indications for mitral valve surgery (repair if possible) include these:

1. Balloon commissurotomy for symptomatic patients with severe MS and favorable morphological features
2. Surgery in symptomatic patients with severe MS who are not high risk and not candidates for balloon commissurotomy
3. Patients with severe MS who are undergoing other cardiac surgery

The reader is referred to the ACC/AHA guidelines for a discussion of class II heart failure, indications for surgery, and indications for valvotomy.

Aortic Regurgitation

Aortic regurgitation (AR) can be due to disease of the aortic valve, root, or both. Heavily calcified valves do not coapt normally, allowing for regurgitation. Diseases that cause dilation of the aortic root, such as Marfan syndrome or syphilis, often lead to chronic AR. Acute regurgitation occurs following trauma, endocarditis, or aortic dissection. Regardless of the cause, AR results in volume overload of the LV. During diastole, the low-pressure ventricle is filled with oxygenated blood through the insufficient valve. Slow heart rates with long diastolic time allow more regurgitation to occur.

In response to the increased volume, the LV dilates and undergoes eccentric hypertrophy. These patients often have massive LVs as their disease progresses. Ventricular function eventually declines, leading to elevated LA pressure, pulmonary edema, and LV failure. Angina can occur, as myocardial oxygen demand is increased in the hypertrophic heart, but the low aortic diastolic pressure limits oxygen delivery.

Poorly tolerant of bradycardia, patients with AR should be maintained at a heart rate in the high normal range (80-100 beats/min). Acute elevations in systemic blood pressure will increase regurgitation and should be avoided. Maintenance of preload is important, as these patients have sustained their cardiac output with a compensatory increase in preload. Aortic valve surgery is a class I indication for chronic AR for the following:

1. Symptomatic patients with severe AR
2. Asymptomatic patients with severe AR and an ejection fraction of less than 0.5
3. Patients with severe AR who are undergoing coronary artery bypass grafting (CABG) or other cardiac surgery

The reader is referred to the ACC/AHA guidelines for a discussion of class II indications for chronic AR and indications for acute AR.

Mitral Regurgitation

Mitral regurgitation (MR) can occur acutely or over time and is caused by a large number of disorders. Chronic MR is very common, with an estimated incidence of 2% to 3%. Rheumatic fever is the most common cause of MR in the developing world, but degenerative disease is more commonly seen in the United States. Degenerative MR is usually due to leaflet abnormalities, such as

seen in mitral valve prolapse, or dilation of the mitral annulus, which often occurs in conjunction with ischemia and ventricular remodeling. Acute MR can occur secondary to ischemia and rupture of the papillary muscles, endocarditis, or trauma.

An incompetent mitral valve allows an alternative pathway for blood flow following ventricular contraction. This leads to a reduction in forward stroke volume and an increase in LA volume. Enlargement of the LA ensues, predisposing to atrial arrhythmias. The LV undergoes eccentric hypertrophy, allowing for maintenance of cardiac output even as forward stroke volume decreases. The contractility of the LV eventually decreases, and the regurgitant volume often exceeds the forward stroke volume.

In chronic MR, the highly compliant LA is able to accommodate the regurgitant volume without elevated pressures. In time, however, the LA is overwhelmed, leading to symptoms of left-sided heart failure and low cardiac output. Acute MR results in pulmonary congestion and edema, because the LA does not have sufficient time to dilate.

Goals of therapy in MR are to reduce the amount of regurgitant volume and control symptoms. Blood always flows down pressure gradients; therefore, low systemic vascular resistance promotes forward blood flow. Acute elevations in blood pressure should be treated promptly. Much like Aortic Insufficiency (AI), MR is worsened with slower heart rates, and bradycardia should be avoided. Atrial fibrillation is a frequent comorbidity in the patient with MR, due to LA dilation, and may be refractory to conventional treatment. Class I indications for mitral valve surgery (repair if possible) include these:

1. Symptomatic patients with severe MR and ejection fraction greater than 30%

2. Asymptomatic patients with severe MR and an ejection fraction between 0.3 and 0.6 and/or with an LV and systolic dimension of 40 mm or less

A discussion of class II indications can be found in the ACC/AHA guidelines.

AORTIC DISSECTION

Aortic dissection is uncommon but is frequently fatal. The incidence of aortic dissection in the United States is approximately 2,000 cases per year. Dissection often causes death before arrival to the hospital or before diagnosis, but late

sequelae are also responsible for high morbidity and mortality.

Aortic dissection is characterized by rupture of the intima and separation of the layers of the aortic wall. A tear in the intima allows blood to enter the aortic wall, further separating the intima and media and causing propagation of the dissection. Blood flow in the newly created false lumen often obstructs flow to branches of the aorta, causing numerous perfusion abnormalities and metabolic derangements.

Risk factors associated with aortic dissection include male gender, hypertension, family history, history of aortic aneurysm, and illicit drug abuse. Aortic cannulation during cardiopulmonary bypass (CPB) is known to cause aortic dissection (**Table 1**).

Table 1. Risk Factors for Aortic Dissection

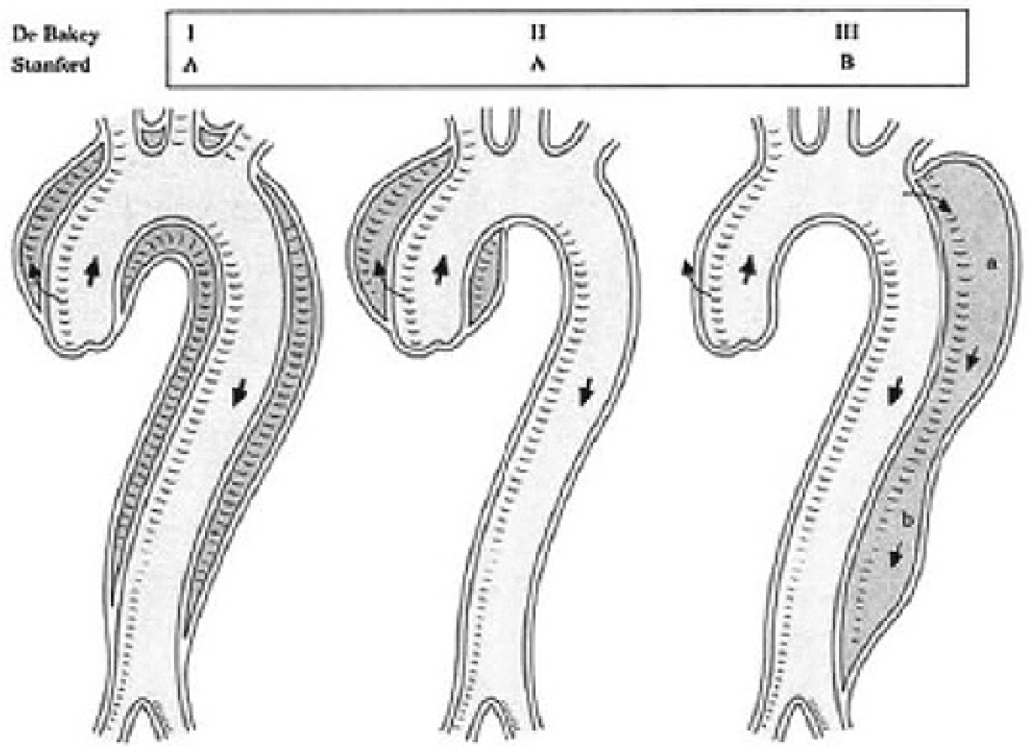
Hypertension
Congenital factors (bicuspid aortic valve)
Pregnancy
Crack cocaine use
Connective tissue disease
Ehlers-Danlos
Marfan
Loeys-Dietz

Types of Dissection

Aortic dissection is acute if diagnosis is made within 2 weeks of the onset of symptoms. Two anatomic classification systems exist: DeBakey and Stanford (**Figure 1**). The DeBakey system entails 3 classes of dissection: class I involves both the ascending and descending aorta, class II involves only the ascending aorta, and class III involves only the descending aorta. The Stanford system includes type A, which involves the ascending aorta, and type B, which involves the aorta distal to the left subclavian. These systems are not perfect; frequently, dissections do not fit into any of these classification schemes. Type A dissections

are more common than type B and have a grimmer prognosis.

Figure 1. Illustration of the Stanford and DeBakey classifications of aortic dissection



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Immediate morbidity from aortic dissection can be as high as 20%. In dissections involving the ascending aorta and arch, mortality increases 1% to 2% every hour, leading to 25% mortality at 24 hours and 50% at 48 hours. Immediate cause of death is commonly myocardial infarction, severe AR, and aortic rupture leading to tamponade. Delayed morbidity and mortality (>24 hours) are usually due to organ malperfusion. Type B dissections are commonly treated medically and have improved survival compared with surgical repair of type A or B dissections. Studies have shown a 13% in-hospital mortality for type B dissections; of these patients, 32% had undergone surgical repair of the dissection.

Treatment of the Patient With Acute Aortic Dissection

Presentation of the patient with acute dissection is variable, often causing the diagnosis to be delayed or missed. Patients frequently present with abrupt chest

and/or back pain, often described as sharp, ripping, or tearing. Hypotension, when present, is an ominous sign, although patients are more frequently hypertensive. Other signs and symptoms are overt heart failure due to severe AR, diaphoresis, and unequal peripheral pulses. Because of the nonspecificity of symptoms, appropriate imaging must be used to confirm suspicion. Chest radiograph and electrocardiographic changes, although frequently present, are nonspecific. Computed tomography (CT), magnetic resonance imaging, transesophageal echocardiography (TEE), and angiography are currently the most used modalities. Helical CT has greater than 80% sensitivity and specificity, is readily available and rapidly performed, and is the most common test used to detect aortic dissection. The inability to detect a dissection in the ascending aorta is perhaps the only limitation of CT. Magnetic resonance imaging has greater than 95% sensitivity and specificity in the detection of dissection and allows accurate assessment of involvement of branch vessels. However, magnetic resonance imaging is not always available and has a long study time, preventing it from being a first-line diagnostic modality in the unstable patient. TEE is an appropriate choice in the diagnosis of aortic dissection but is not used frequently, because the patient must be sedated and the appropriate physicians must be available to perform the study. Also, much of the aortic arch is not visualized with TEE, because the trachea comes between the probe and the aorta. Mortality from acute aortic dissection is due to several mechanisms. Frank rupture can occur following dissection, resulting in tamponade (if rupture into the pericardium) or hemorrhagic shock. Overt heart failure occurs when the dissection directly involves the aortic valve leaflets or when the dissection flap prolapses through the aortic valve, causing severe acute AR. Dissections can propagate retrograde, dissecting through the coronary arteries, obstructing blood flow, and causing myocardial ischemia. Dissections can disrupt blood flow to any artery of the aorta, which can impair perfusion to the brain, viscera, and limbs, causing end-organ ischemia and infarction.

Following successful diagnosis of acute aortic dissection, rapid management is essential for continued survival. Immediate administration of antihypertensive therapy is a requirement for all patients who are not hypotensive. The goals of antihypertensive therapy are not only to reduce arterial blood pressure but also to reduce dP/dt, or the shear force caused by LV contraction. Systolic arterial blood pressure should be maintained as low as possible, while still allowing adequate organ perfusion. β-Blockers are frequently the first-line antihypertensive used. Short-acting IV forms such as esmolol are easily titratable and reduce both blood pressure and contractility. Sodium nitroprusside is often used concurrently but

should not be used as a single agent, as it frequently results in reflex tachycardia. Calcium channel blockers can be used, as they are both vasodilators and negative inotropic agents.

Following stabilization, management strategies differ based on the type of dissection. Proximal dissections involving the ascending aorta and arch are indications for surgical management. Few exclusions exist, as mortality is high without surgery. Intraoperative mortality for acute aortic dissection ranges from 10% to 15% in straightforward repairs to upward of 30% in patients with ongoing complications. Risk factors for surgical mortality include tamponade, end-organ ischemia, renal dysfunction, and pulmonary disease. The surgical approach is usually through a median sternotomy. Because multiple branches may be involved, different techniques to protect from ischemia have been used intraoperatively, including CPB, partial left-sided heart bypass, deep hypothermic circulatory arrest, and retrograde perfusion. Goals of surgery are aimed at prevention of fatal sequelae, namely AR, tamponade, and aortic rupture. This is accomplished by primary repair of the intimal tear, replacement of the dilated aorta, and aortic valve repair or replacement.

Management of distal aortic dissection is rapidly evolving, due to the increased use of endovascular repair. In the past, uncomplicated distal dissections were managed medically, and surgery was considered only for complicated dissections (in rapidly expanding, impending rupture, ongoing pain, or limb or organ ischemia). However, endovascular repair is now considered first-line therapy for complicated dissections and is being increasingly used in uncomplicated dissections as well. Endovascular repairs of aortic dissections are becoming increasingly common. Through femoral artery access, a synthetic graft can be placed over the intimal tear, preventing further communication to the false lumen and improving blood flow to the viscera. Goals of endovascular repair are to restore malperfusion, exclude or close the primary tear, and obliterate the false lumen.

Although advances have been made in diagnostic and therapeutic management of acute aortic dissection, mortality remains high. In-hospital mortality for acute dissections remains between 25% and 30%. Following initial treatment, patients should be managed aggressively with antihypertensive agents. Serial imaging of the aorta is necessary to monitor for further aneurysm formation.

CARE OF THE POSTOPERATIVE CARDIAC PATIENT

Cardiac surgery is unique given the hemodynamic, pulmonary, and inflammatory changes that occur intraoperatively. It is only natural, then, that the postoperative course is unique in its challenges.

Most cardiac surgical patients are elderly and present with multiple comorbidities. In addition, many of the initial abnormalities, both cardiac and noncardiac, will be unchanged postoperatively and perhaps even worsened. These factors influence the care of patients after cardiac surgery.

Intraoperative Details and the Effects of Cardiopulmonary Bypass

Once a patient arrives in the ICU from the operating room, information regarding the operative course must be garnered in a timely and organized fashion.

The procedure that was performed must be determined. Frequently, procedural changes are made intraoperatively, based on echocardiographic or surgical findings. Intraoperative details of the procedure performed directly affect the postoperative management. “Open-heart” procedures are associated with different risks and complications than procedures that are not intracardiac. Most procedures are, in fact, open heart; the exception is CABG. When the heart (or aorta) is opened, whether to repair a valve or abnormal opening (ventricular septal defect) or to provide mechanical ventricular support, air can be entrained into the circulation. Careful examination of air by TEE and de-airing procedures by the surgeon are important to prevent air embolus following separation from CPB.

Other procedural details to note include type and size of valve (bioprosthetic, mechanical), incidental findings, and other unexpected factors. These factors can include arrhythmias (and their associated treatments) experienced following bypass, long-acting drugs given by the anesthesia team, or concerns regarding pulmonary function and compliance. The anesthesia provider will be able to give a full echocardiographic report if intraoperative echocardiography is used. Intraoperative TEE can provide information regarding the structural integrity of the valvular structures, overall function of the left and right side of the heart, and regional wall motion abnormalities. TEE is commonly used to guide inotropic support following CPB and can offer insight into issues regarding volume loading, right-sided heart dynamics, and LV function.

Use of and duration of CPB are important details in patient management after

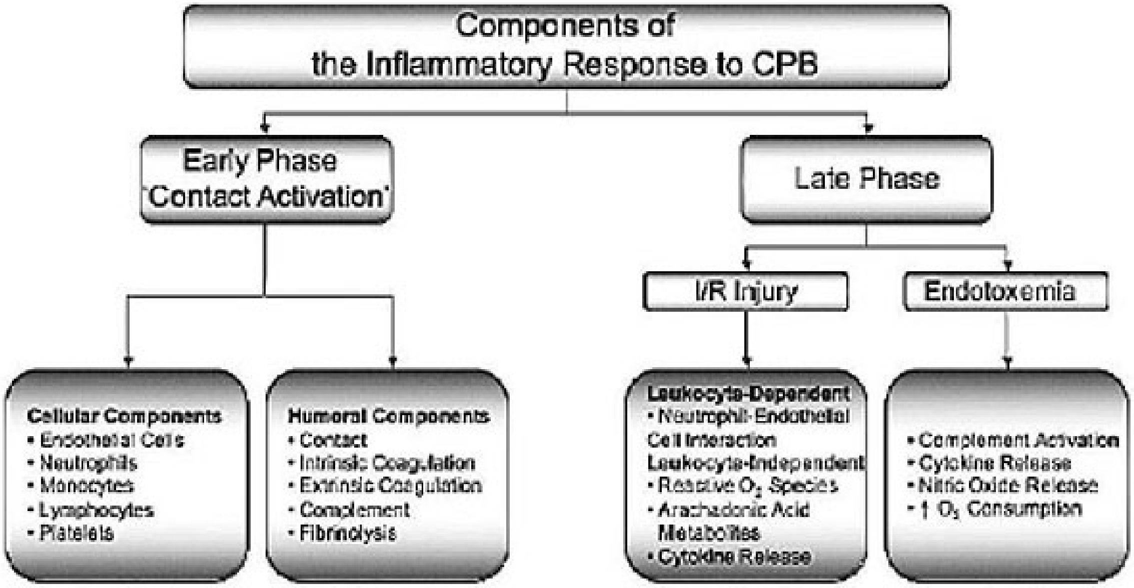
cardiac surgery. The effects of CPB on neurological status, renal function, coagulopathy, and pulmonary function have been studied since the advent of extracorporeal circulation, but many questions remain. Therefore, it is important to have a basic knowledge of the mechanisms of such widespread derangements.

CPB causes a systemic reaction that has many adverse effects (**Table 2**). Stimuli for this response are numerous and include hypothermia, hemodilution, nonpulsatile flow, and exposure to the bypass circuit. Both endocrine and immunological responses are seen and will be briefly discussed, although a full discussion of the immune response is beyond the scope of this chapter. Ischemia-reperfusion injury is also a concern. The activation of these pathways complicates recovery and can lead to the development of acute lung injury, renal failure, altered hepatic function, coagulopathy, and even multiple organ failure (**Figure 2**). The intricate cascade of events following CPB has many similarities to sepsis.

Table 2. Inflammatory Mediators Associated With Cardiopulmonary Bypass

Complement
Endotoxin
Tumor necrosis factor α
Platelet activating factor
Cytokines
Free radicals
Nitric oxide

Figure 2. Systemic effects of cardiopulmonary bypass



Abbreviations: CPB, cardiopulmonary bypass; I/R, ischemia-reperfusion.

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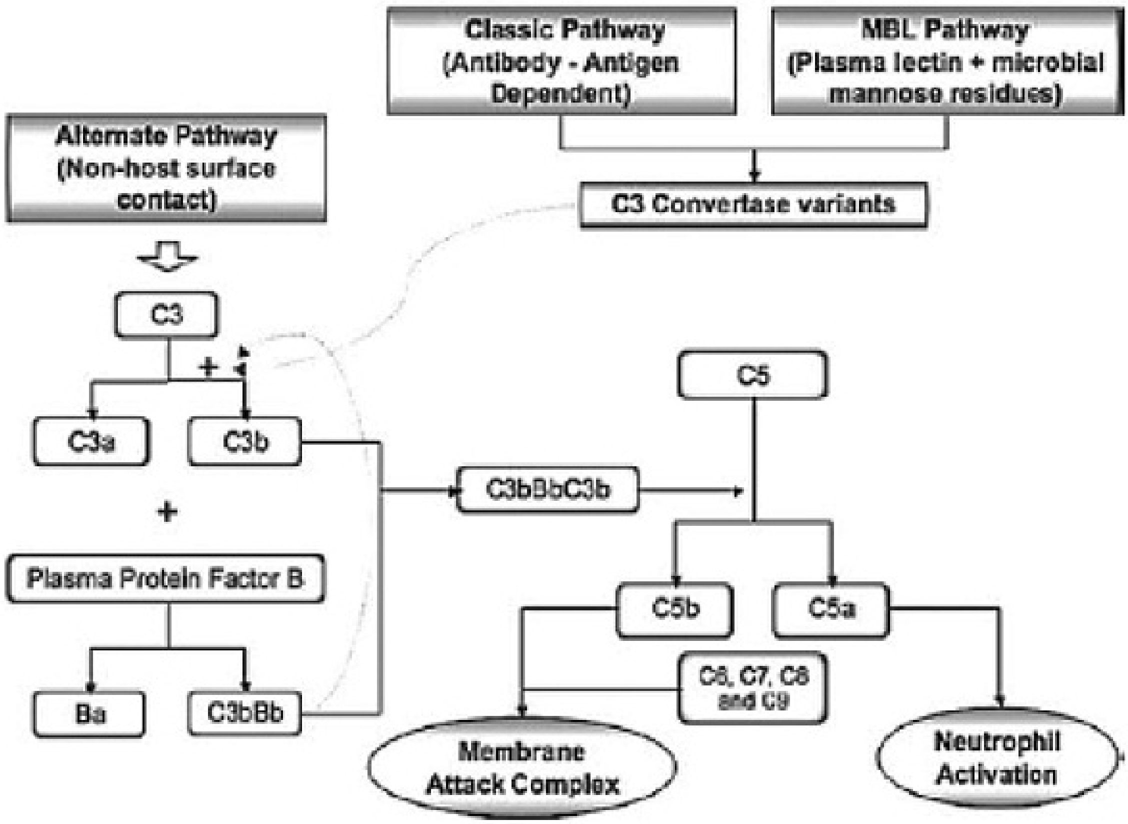
The flow of blood through the extracorporeal bypass circuit activates complement, platelets, neutrophils, and creation of free radicals. The complement system, which consists of many plasma proteins, usually acts as the body's natural defense against many insults. The classic pathway is activated by immune complexes (antibodies bound to antigens). The alternative pathway is activated by microbial cell or nonhost surfaces. The mannose-binding lectin pathway is activated by plasma lectins that bind to mannose (**Figure 3**). It is thought that with the initiation of CPB, complement is activated via the alternative pathway. Activation can also occur through the classic pathway by heparin-protamine complexes. Although the clinical significance of the activation of complement following CPB is uncertain, it has been implicated in the development of acute lung injury as well as continuation of the inflammatory response.

Figure 3. Complement cascade and cardiopulmonary bypass



Abbreviation: MBL, mannose-binding lectin.

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The inflammatory cascade involves the release of endotoxin, which furthers the activation of the inflammatory response. This involves activation of macrophages, production of cytokines, and development of a positive feedback loop involving interleukins and tumor necrosis factor. Cytokines are important in cell regulation and stimulation of T and B cells as well as neutrophil chemotaxis. Much work has been done to identify strategies to reduce this response or to prevent its occurrence, without consensus. The use of corticosteroids before bypass continues to be controversial. Although the effect of a systemic inflammatory response to CPB is itself a significant insult, ischemia-reperfusion injury also plays a notable role in the development of organ failure.

Neurological insult is a well-known risk of cardiac surgery, with an incidence between 5% and 15%. Adverse events include stroke, coma, memory deficits, seizures, and paralysis. The presence of any unexpected neurological outcome has been found to increase mortality and length of stay in the ICU and the

hospital. Predicting which patients are at higher risk for neurocognitive decline is difficult, and the mechanisms are unclear (**Table 3**). It is generally accepted that most strokes are caused by a showering of atherosclerotic emboli, mobilized by surgical manipulation of the aorta. Hypoperfusion also plays a major role in postoperative stroke. In patients with preexisting neurological disease, cerebral blood flow may already be impaired and will only worsen further from nonpulsatile states. Air embolus is always a concern for procedures that require aortotomy or an open heart, as air is entrained into the circulation. In contrast to stroke, air embolus rarely presents with radiological findings and may only present with seizure or delayed emergence from general anesthesia (**Table 4**).

Table 3. Risk Factors for Postoperative Neurocognitive Decline

Age
Aortic atherosclerosis
History of neurological disease
Female gender
Carotid artery disease

Table 4. Air Embolus

Signs and symptoms
Seizures
Delayed emergence
Radiological findings
Focal neurological findings
Treatment
100% oxygen
Hyperbaric oxygen/recompression
Supportive therapy

Acute renal failure following cardiac surgery increases mortality significantly. In a Veterans Administration study, mortality was 63% in postoperative patients requiring dialysis compared with 4% in patients not requiring renal replacement. Numerous trials have shown worsened survival of patients who require hemodialysis while in the ICU. Because of factors such as nonpulsatile flow and hypoperfusion, between 4% and 10% of patients undergoing cardiac surgery with CPB will have acute renal failure postoperatively. Many studies have found that those who suffered a renal insult tended to have longer bypass and aortic cross-clamp times. Intraoperative medications may also play a role: Aminocaproic acid (EACA), an antifibrinolytic agent, has been scrutinized for the high rate of renal failure associated with its use. The intensivist must be cognizant of the possibility of postoperative renal failure and must alter the treatment strategy accordingly.

Ventricular function must be assessed postoperatively and will be the focus of most modes of hemodynamic monitoring throughout the acute postoperative period. Preoperative left and right ventricular function is key to postoperative performance; even though a fixed obstruction to flow is removed (eg, stenotic valve) or volume overload is reduced (eg, a regurgitant lesion or atrial septal defect), the ventricle will not immediately show improvement. Even though hypothermic cardiac arrest is routinely performed, some degree of myocardial dysfunction is present postoperatively. Multiple trials and observations have noted that cardiac function is depressed initially, reaching a nadir from 4 to 6 hours postoperatively but recovering within 24 hours. The mechanism behind the dysfunction is unclear. Current theories include reperfusion injury, the production of oxygen free radicals during bypass, and hypercalcemia following cardioplegia. Again, the preoperative ventricular function is usually the largest contributor to postoperative ventricular function. Intraoperative assessment of cardiac function is through echocardiography, calculation of cardiac output via a pulmonary artery catheter, and direct visualization of the surgical field. Postoperative assessment relies more on measurements of cardiac output via a pulmonary artery catheter, echocardiography, and secondary indirect measures, such as urine output, blood pressure, and heart rate.

Many centers provide inotropic support to all patients who have undergone CPB. Common inotropes include dopamine, dobutamine, epinephrine, and milrinone; vasopressors include norepinephrine, vasopressin, and phenylephrine. A solid understanding of cardiovascular drugs is essential and is beyond the scope of this review. The clinical scenario, such as procedure performed, ventricular function,

and duration of bypass, usually guides selection of inotropes and vasopressors (**Table 5**).

Table 5. Cardiovascular Drugs

Drug	Dosage	Mechanism of Action	Other
Dopamine	2-20 μg/kg/min IV	β and dopaminergic receptors	Significant tachycardia
Dobutamine	2-20 μg/kg/min IV	β	Vasodilation of skeletal muscle vasculature
Epinephrine	0.02-0.2 μg/kg/min IV	α and β	Increased vasoconstriction at higher doses
Norepinephrine	0.01-0.2 μg/kg/min IV	α and β	
Milrinone	0.2-0.75 μg/kg/min IV	Phosphodiesterase inhibition, renal excretion	Inodilator; usually coupled with a β-agonist, bolus dose of 50 μg/kg
Vasopressin	0.04-0.08 U/min IV	Replacement of deficient antidiuretic hormone	Detrimental effects seen at high doses
Epoprostenol	Start at 50 ng/mL/min inhaled and titrate down	Prostacyclin increases cyclic adenosine monophosphate, leading to vasodilation	Concerns for platelet inhibition
Nitric oxide	5-20 ppm inhaled	Signaling molecule, vasodilator	Cost prohibitive

Inotropes improve ventricular contractility. Patients with low cardiac output or index (cardiac index <2 L/min/m^2) should be evaluated for volume status, heart rate and rhythm, and signs of surgical bleeding or tamponade before starting inotropes. Dopamine works on both dopaminergic receptors and β receptors. Dopaminergic receptors are found primarily in the splanchnic circulation and the central nervous system. The activity on the β_1 receptors is responsible for the inotropic and chronotropic effects. Dopamine has fallen out of favor in recent years because of the lack of evidence that splanchnic and renal blood flow is improved with use. Dobutamine is a pure β agonist that improves contractility with some elevation of heart rate. Although there is less affinity to the β_2 receptors, vasodilatation of the skeletal muscle beds tends to offset any increase

in systemic blood pressure.

Epinephrine is a naturally occurring catecholamine that acts on both α and β receptors. Epinephrine is much more potent than dobutamine and tends to cause a more robust increase in blood pressure, especially at higher doses. Both dobutamine and epinephrine can be arrhythmogenic; removal of the offending agent is sometimes the only way to prevent the arrhythmia.

Milrinone is a phosphodiesterase inhibitor that does not rely on either α- or β-receptor stimulation. Through inhibition of phosphodiesterase III and increased levels of cyclic adenosine monophosphate, intracellular cardiac calcium stores are increased, promoting increased contractility. In vascular beds, increased calcium stores lead to increased vasodilatation and decreased peripheral vascular resistance. A loading dose of 50 μg/kg is given, although this may be decreased or omitted in the presence of renal failure, because milrinone is renally excreted.

Vasopressors commonly used in cardiac surgical patients include norepinephrine, vasopressin, and phenylephrine. All vasoconstrictors can cause peripheral vasoconstriction, increased afterloads, and organ hypoperfusion. Therefore, fluid status, cardiac output, and tissue perfusion must be frequently assessed when any vasoconstrictor is used. Norepinephrine is a naturally occurring catecholamine and the precursor to epinephrine. A potent α agonist at higher doses, norepinephrine also has significant β-agonist effects. Phenylephrine is a pure α agonist that has no β-receptor effects. There are specific circumstances when phenylephrine is the drug of choice. These include tetralogy of Fallot and hypertrophic cardiomyopathy and evidence of systolic anterior motion of the mitral valve. Arginine vasopressin is an exogenous preparation of antidiuretic hormone (ADH), with a relatively new indication for the treatment of vasodilatory shock and heart failure. It is thought that some patients who are refractory to traditional treatment of hypotension and vasodilatory shock have a deficiency of endogenous ADH. Therefore, exogenous replacement of vasopressin is beneficial. Although many of the above-mentioned pharmacological agents are able to support cardiac function satisfactorily, occasionally attention must be brought to the right ventricle (RV). The RV is not merely a carbon copy of the LV; its form and function are quite different, and means of supporting it can be quite different as well. The RV is structured for compliance, because it receives the venous return from the body. Usually pumping into the low-resistance pulmonary vasculature, the RV does not have the same muscular structure as the LV. The RV fails when it can no longer overcome elevated vascular resistance of the lungs. This is usually manifested by

an acute dilatation of the ventricle, with increasing central venous pressure. The LV suffers from decreased forward flow from the lungs, and cardiac output is decreased.

Failure of the RV is treated by the following:

1. Improving RV contractibility
2. Improving mean arterial blood pressure and RV perfusion
3. Optimizing RV filling pressure
4. Decreasing PVR

Dobutamine and milrinone are the most common inotropes used to treat RV failure. Often, a vasoconstrictor (norepinephrine or vasopressin) is used with an inotrope to increase mean arterial blood pressure (and therefore RV perfusion pressure). Preload optimization is difficult and is best guided by echocardiography. Too much preload will dilate the RV, which moves the ventricular septum to the left, improving LV filling; without enough preload, the RV cannot eject.

Anything that increases PVR (hypothermia, hypoxia, acidosis, hypercarbia) must be avoided or treated. Epoprostenol, or inhaled prostacyclin, and nitric oxide are both inhaled agents that have been found to decrease PVR, thus decreasing the afterload against which the RV must work. Studies have shown that, inhaled prostacyclin decreases mean pulmonary artery pressure without decreasing systemic blood pressure, at a much lower price than nitric oxide. Side effects of epoprostenol are minimal, but concerns for platelet inhibition cause some practitioners to be wary.

Bleeding is a major concern during the immediate postoperative period. The cause of bleeding is often multifactorial; hypothermia and thrombocytopenia are quite common. A surgical source of bleeding must be ruled out; anastomotic leaks are often the culprit, although frequently no source is found. In the meantime, aggressive treatment of bleeding and coagulopathy is essential. This usually begins in the operating room, where several different fibrinolytic agents are used. EACA and tranexamic acid (TXA) are the agents most commonly used today. Both drugs are lysine analogs and effectively inhibit plasmin, thus preventing the degradation of fibrin. Both drugs are routinely bolused prior to commencement of CPB, although firm dosing protocols for TXA have not been

established. TXA has been favored in recent years, given a significant incidence of renal failure in patients receiving EACA, but concerns of increased seizures with TXA have arisen. In a retrospective analysis of 600 patients undergoing cardiac surgery, significantly more seizures were reported in the patients receiving TXA, yet acute renal failure was more prevalent in the EACA group. Aprotinin, a protease inhibitor that acts on factor XIIa, was used in cardiac surgery in the past but has been permanently removed from use because of unacceptable rates of renal failure, myocardial infarction, and stroke. Desmopressin is a derivative of ADH, much like arginine vasopressin, except desmopressin raises plasma levels of factor VIII and von Willebrand factor by release from endothelial cells. In the late 1970s, desmopressin was used to treat hemophilia A and other von Willebrand disease. Desmopressin raises levels of factor VIII and von Willebrand factor in healthy patients with normal levels of these factors. Because of this, desmopressin may improve platelet function following cardiac surgery. However, studies of prophylactic use of desmopressin have not been conclusive.

Many of the aforementioned drugs are used prophylactically in the cardiac surgical suite. Recombinant factor VIIa (rVIIa) is a fairly new therapy that has been used off label in cardiac, trauma, and spinal surgery. Initially developed for use in hemophilia A and B with the presence of inhibitors, rVIIa has a mechanism of action that is unclear. It is an expensive drug, and the potential side effects could be disastrous. Although multiple studies showed no increased thromboembolic events in patients receiving rVIIa, other studies and a recent meta-analysis showed that in patients treated with rVIIa, especially the elderly, had a significantly higher incidence of arterial thromboembolic events. Therefore, rVIIa may be useful in cases of bleeding refractory to standard therapy, but the risks must be considered prior to administration.

In the immediate postoperative period, the ICU team must be vigilant for the development of cardiac tamponade. Tamponade occurs more frequently in patients undergoing valve surgery than CABG and in those who have recently received a dose of aspirin, warfarin, or heparin. Tamponade in the postsurgical patient can be difficult to diagnose, because the usual hemodynamics have been altered significantly. Many of the classic symptoms are absent, and suspicion may be the only indicator. Frequently, tamponade is an empirical diagnosis in the patient with worsening cardiac function or low cardiac output. Transthoracic echocardiography is not always useful in postoperative cardiac patients, as bandages, drains, and wires frequently obscure the usual windows. In this

situation, TEE is usually the better diagnostic tool. Tamponade in the postoperative patient can be acute or delayed and can be a regional issue, such as when a large clot abuts the RV. Surgical exploration is the basis of treatment in all cases of post–cardiac surgery tamponade.

Atrial Fibrillation

Atrial fibrillation (AF) is a common arrhythmia following cardiac surgery. It is associated with increased morbidity and mortality and length of stay following surgery as well as requirements for further follow-up, medications, and monitoring following discharge. The incidence in postoperative cardiac patients (defined as time of surgery to hospital discharge) ranges between 20% and 40%. This is in stark contrast to the incidence of AF in the general population—approximately 1% to 2%. The cause of postoperative AF remains unclear. Speculation includes exposure to CPB, β-blocker withdrawal, or manipulation of the right atrium. A popular theory is that patients have an electrophysiological abnormality that presents, with the appropriate trigger, as AF.

Much work has been done to predict AF in patients following cardiac surgery, without much success. Age has been found to be the strongest predictor, which is a shared risk factor of the general population. Other risk factors with some potential predictive power include hypertension, the presence of chronic obstructive pulmonary disease, and bypass time. Valve surgery has the greatest incidence of AF postoperatively, compared with CABG and aortic surgery. With this knowledge in mind, the intensivist must be vigilant for the development of AF in the postoperative patient.

Extensive discussion of the treatment of AF is covered elsewhere in this text; only a cursory overview is presented here. AF is most common on postoperative days 2 and 3, a time when discharge planning is often underway, which is delayed by AF. Rapid response to arrhythmia must occur, as these patients frequently do not tolerate the hemodynamic perturbations associated with AF. Electrical cardioversion is always the first line of treatment in an unstable patient with new-onset AF, and delay in treatment must be avoided. Pharmacological cardioversion can be accomplished with a number of drugs; selection must be tailored to the patient and clinical scenario. A combination of pharmacological and electrical cardioversion may increase success rates. Refractory AF may require long-term use of antiarrhythmic agents.

Postoperative Sedation and Analgesia

As medicine and cardiac surgery become more streamlined and efficient, postoperative care must do so as well. Sedation and analgesia must be tailored to the patient and procedure to provide for the most safe and expeditious extubation and ICU discharge. Frequently, these plans are put into action in the operating room by the anesthesia care team, but such plans must be carried out and changed as needed in the ICU. Many drugs are available for postoperative sedation and analgesia, so the intensivist has numerous options. Several recent studies have evaluated patient-controlled sedation and analgesia and sedation protocols in an attempt to individualize therapy. Each patient must have a sedation and analgesia plan that will provide adequate pain relief while allowing for neurological evaluation, appropriate interaction, and efficient use of ICU time and resources.

SUMMARY

- Aortic stenosis: Hemodynamic management includes avoiding tachycardia, maintaining normal sinus rhythm, and ensuring adequate preload and increased afterload.
- Mitral stenosis: Hemodynamic management includes avoiding tachycardia, maintaining normal sinus rhythm, and ensuring adequate preload and normal afterload.
- Aortic regurgitation: Hemodynamic management includes avoiding bradycardia, maintaining normal sinus rhythm, and ensuring adequate preload and low afterload.
- Mitral regurgitation: Hemodynamic management includes avoiding bradycardia, maintaining normal sinus rhythm, and ensuring adequate preload and low afterload.
- Aortic dissection: Stanford A and DeBakey I and II involve the ascending aorta and are surgical emergencies. Stanford B and DeBakey III involve only the distal aorta and are medical emergencies, unless specific organs need revascularization.
- Cardiopulmonary bypass: Extracorporeal circulation is used in cardiac surgery that activates coagulation, endocrine, inflammation, complement, and ischemia-reperfusion pathways.

- Cardiac tamponade post cardiac surgery: This can be a regional tamponade effect and can only be ruled out using TEE in postoperative cardiac surgical patients.

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CHAPTER 14

Hypertensive Crises

Amanda M. Gomes, MD

Key words: hypertensive emergency, hypertensive urgency

Hypertension is a common clinical disorder estimated to affect approximately 30% of adults in the United States. The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure classifies hypertension using 3 stages: prehypertension, stage 1, and stage 2.

Hypertensive crises are defined as severe elevations in blood pressure. A hypertensive emergency is a severe elevation in blood pressure associated with the presence of acute end-organ damage. Hypertensive emergencies require immediate control of blood pressure, within 2 hours, to prevent further organ damage. Treatment requires IV medications with invasive monitoring (arterial line) in an ICU. The principal systems susceptible to acute end-organ damage from severe elevations in blood pressure include the central nervous, cardiovascular, and renal systems (**Figure 1**). Several clinical situations are associated with hypertensive emergencies (**Table 1**).

Figure 1. End-organ failure associated with hypertensive emergencies

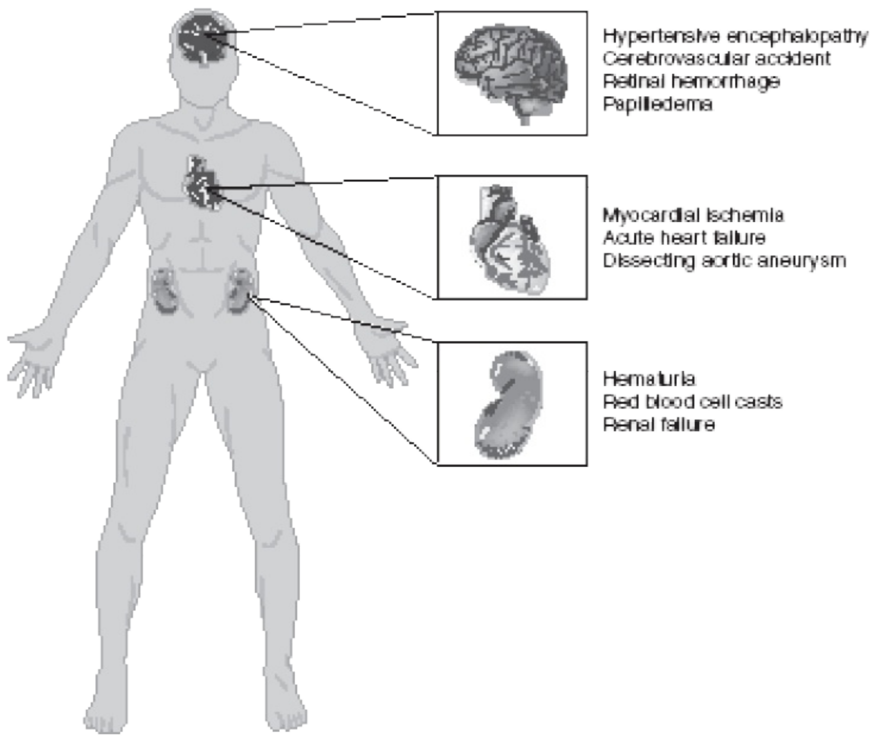


Table 1. Clinical Scenarios Associated With Hypertensive Emergencies

Acute aortic dissection
Acute left ventricular failure
Acute myocardial infarction
Acute renal failure
Cerebrovascular accident
Catecholamine excess states
Hypertensive encephalopathy
Postoperative hypertension
Preeclampsia/eclampsia

Hypertensive urgency is defined by severe elevations of blood pressure without evidence of acute end-organ damage. In the absence of acute end-organ damage, blood pressure reductions can be achieved gradually over 24 to 48 hours. Treatment of hypertensive urgencies can usually be achieved with oral

medications and does not require invasive hemodynamic monitoring in an ICU. Hypertensive urgencies can be associated with chronic stable organ dysfunction, such as stable angina, chronic renal insufficiency, or previous cerebrovascular accident, without evidence of acute end-organ damage.

APPROACH TO MANAGEMENT

Unfortunately, few clinical trials are available to guide the clinician in managing patients with hypertensive emergencies. However, a systematic approach with consideration of the underlying pathophysiological process can help the clinician avoid common pitfalls in the management of patients with hypertensive crises. The most common pitfall in treating patients with hypertensive crises involves treating relative to blood pressure without evaluating the patient for acute end-organ damage. This pitfall is usually associated with the inappropriate use of IV medications that carry the potential for precipitous and harmful decreases in blood pressure. A methodical approach to severe elevations in blood pressure can help establish safe and effective treatment. The clinician should address 3 fundamental questions:

1. Should the blood pressure be lowered acutely?
2. How much should the blood pressure be lowered?
3. Which medication should be used to lower the blood pressure?

Should the Blood Pressure Be Lowered Acutely?

To answer this question, the clinician must determine whether there is evidence of acute end-organ damage. In patients with hypertensive emergencies (presence of acute end-organ damage), the blood pressure should be lowered acutely to a safe target to prevent further end-organ damage. A focused history should determine any previous diagnosis of hypertension, the medication history, the use of illicit drugs or over-the-counter agents with potential hypertensive effects, and the presence of symptoms consistent with neurological, visual, cardiac, or renal dysfunction. The blood pressure should be measured in both upper extremities, and pulses in all extremities should be checked, as inequalities in blood pressure or pulses can exist with aortic dissection. A thorough neurological and cardiopulmonary examination should be conducted to evaluate possible signs of end-organ failure such as altered mentation, new focal neurological deficits, or cardiogenic pulmonary edema. The clinician should

conduct a fundoscopic examination of the eyes, looking for signs of acute papillary edema or new retinal hemorrhages. An electrocardiogram to rule out active ischemia and a chest radiograph to assess for pulmonary edema or signs of aortic abnormalities are helpful to evaluate the cardiopulmonary system. Abnormalities in the serum urea nitrogen, creatinine, and urine analysis (red blood cell casts) suggest renal involvement. Additional tests may be indicated based on the individual characteristics of each case.

The presence or absence of acute end-organ damage should dictate the acuity with which blood pressure reduction should be achieved. If the clinical evaluation provides evidence of acute end-organ damage, the patient’s blood pressure should be lowered acutely. However, if a careful, systematic clinical examination and diagnostic tests do not show evidence of acute end-organ damage, the blood pressure does not require immediate reduction.

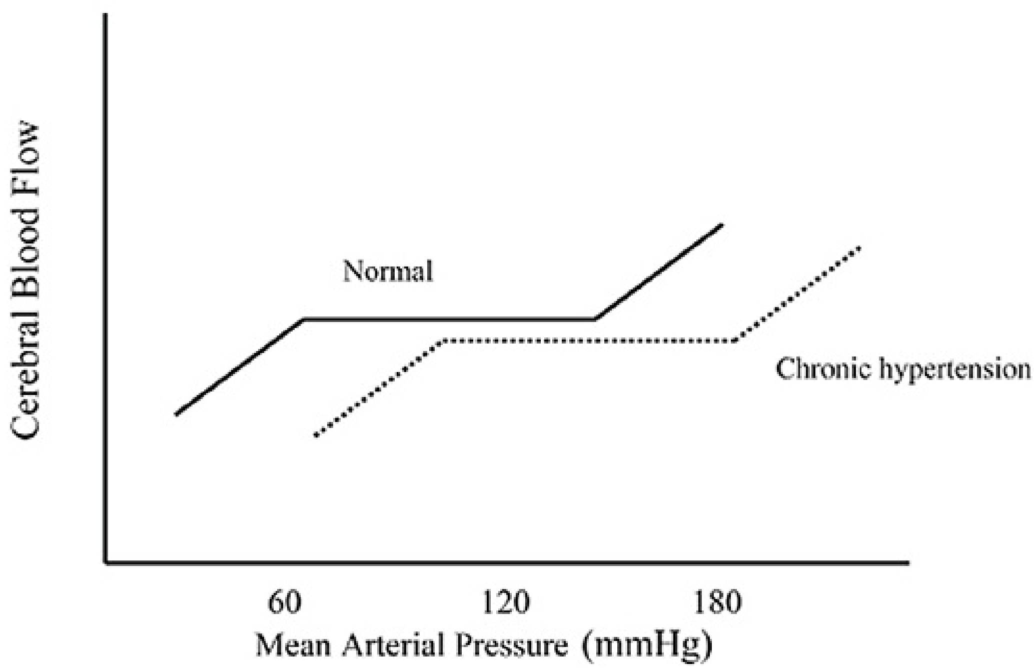
How Much Should the Blood Pressure Be Lowered?

If the blood pressure requires immediate reduction, the next step is to establish a safe therapeutic target for the blood pressure. The goal for treating hypertensive emergencies is to lower the blood pressure to a level that prevents ongoing acute end-organ damage and avoids iatrogenic damage due to precipitous decreases in the blood pressure causing hypoperfusion to organs. Most experts would recommend that for most hypertensive emergencies, the goal should be to lower the mean arterial pressure (MAP) by 15% to 25% over a period of several minutes to hours, depending on the clinical situation. Reducing the blood pressure to achieve normal levels may be warranted in special situations, such as patients with aortic dissection or previously normotensive patients with a postoperative hypertensive emergency. Understanding autoregulation of blood pressure in normal states and in patients with chronic hypertension is essential to achieving these goals.

Different organs have the ability to autoregulate and maintain a constant blood flow through a range of MAPs. Under normal conditions, cerebral autoregulation will keep blood flow constant between MAPs of 60 and 150 mm Hg. When the MAP decreases, cerebral arteries will dilate; if the MAP increases, these arteries will constrict to maintain constant blood flow to the brain. Decreases in the MAP below the lower limit of autoregulation will lead to hypoperfusion resulting in brain ischemia. Increases in the MAP above the higher limit of autoregulation may lead to hypertensive encephalopathy. With chronic hypertension, compensatory functional and structural changes occur in the vasculature. These

changes shift the autoregulatory curve to the right. The autoregulatory curve for cerebral blood flow in healthy individuals and in patients with chronic hypertension is shown in **Figure 2**. Hence, patients with chronic hypertension will have a higher tolerance to elevated blood pressures since their autoregulatory curve is shifted to the right. This shift explains why many patients present with severely elevated blood pressures and no evidence of acute end-organ damage. However, rapid reduction of blood pressures to achieve normal levels can result in pressures below the lower autoregulatory capacity of the circulation in a chronically hypertensive patient. This phenomenon explains the hypoperfusion of vital organs and development of renal failure and/or cerebral ischemia often seen when the blood pressure is lowered too far or too fast in this population.

Figure 2. Cerebral blood flow autoregulation for normotensive and chronic hypertensive states



Which Medication Should Be Used to Lower Blood Pressure?

Once a decision to treat a hypertensive emergency has been made and a target blood pressure has been established, physicians must decide on the most appropriate medication for each individual patient. A limited number of studies have compared agents in terms of clinical outcomes. With no clear outcome data, drug selection is based on the clinical scenario, pharmacological characteristics of the drug, and availability. The following is a discussion of the parenteral agents most commonly used in treating hypertensive emergencies (in

alphabetical order).

Clevidipine

Clevidipine is a relatively new agent approved for use in treating severe hypertension during surgery. It is an ultra-short-acting calcium channel antagonist. Clevidipine has vasoselective properties with a rapid onset of action and a very short half-life (<1 minute). It is metabolized by red blood cell esterases and, therefore, is not affected by renal or hepatic failure. Clevidipine reduces blood pressure by a direct and selective effect on arterioles. It does not produce reflex tachycardia, and its effect on reducing afterload is often associated with increased cardiac output. Clevidipine is administered intravenously as a continuous infusion. The initial dose is 1 to 2 mg/h with adjustments as needed to obtain the desired response in blood pressure. The maintenance dose is 4 to 6 mg/h; however, higher doses may be required in certain clinical situations. Small studies have compared clevidipine to nitroprusside for treatment of severe hypertension in anesthetized patients undergoing surgery. These studies showed that clevidipine had similar effects on blood pressure control with less effect on cardiac filling and heart rate. Although clevidipine has not been studied extensively in other clinical situations, its characteristics make it an attractive option for the treatment of hypertensive emergencies outside of the operating room. More recently, clevidipine has received increased attention as an agent for use in neurological hypertensive emergencies.

Esmolol

Esmolol is an ultra-short-acting, cardioselective, β-adrenergic agent that can be administered intravenously for the treatment of hypertensive emergencies. It has a rapid onset of action (within 2 minutes) and a short duration of action (approximately 20 minutes). Esmolol is rapidly metabolized by red blood cells and is not dependent on renal or hepatic function. The usual loading dose is 0.5 mg/kg followed by a maintenance infusion of 25 to 300 μg/kg/min titrated to the patient's individual response. Esmolol has been found to be effective in controlling postoperative hypertension and tachycardia in several clinical studies. It is most useful in situations where both blood pressure and tachycardia are present and the patient has no contraindications to β-blockade (ie, severe systolic cardiac dysfunction or asthma). Esmolol may be used in conjunction with other agents to achieve an enhanced response.

Fenoldopam

Fenoldopam is a selective dopamine agonist that causes systemic and renal vasodilation. It has a rapid onset of action (5 minutes) and a relatively short duration of action (30-60 minutes). It is rapidly metabolized by conjugation in the liver to inactive metabolites that are excreted by the kidney. The plasma elimination half-life is approximately 5 to 10 minutes. Fenoldopam is administered as a continuous infusion (without a bolus dose) at 0.1 μg/kg/min and is titrated by 0.05 to 0.1 μg/kg/min, with a maximum dose of 1.6 μg/kg/min. Common adverse effects of the drug are related to its vasodilator properties and include hypotension, headache, reflex tachycardia, and flushing. It can also cause an increase in intraocular pressure and should be avoided in patients with glaucoma. Clinical studies in patients with hypertensive emergencies have found that the efficacy of fenoldopam is comparable to that of sodium nitroprusside. Because of its effects on the renal vasculature and its ability to increase urine output, fenoldopam has been proposed as a renal-protective drug. In the setting of a hypertensive emergency, protective effects of fenoldopam on renal function have not been confirmed. However, because fenoldopam does not affect renal function adversely and does not have increased toxicity in patients with renal failure, it may be a useful alternative to sodium nitroprusside in patients with hypertensive emergency and renal failure.

Labetalol

Labetalol is a combined α- and β-adrenergic receptor blocker approved for both oral and IV use in the treatment of hypertension. Labetalol lowers blood pressure by decreasing systemic vascular resistance by α_1-adrenergic blockade. This agent reduces peripheral vascular resistance while maintaining cerebral, renal, and coronary blood flow. Unlike other β-blockers, labetalol does not reduce cardiac output. When administered intravenously, it has a rapid onset of action (2-5 minutes) with peak hypotensive effect occurring within 5 to 10 minutes and lasting 2 to 4 hours. The drug is primarily metabolized by the liver and has a plasma elimination half-life of approximately 5 hours. Labetalol is usually administered intravenously as a loading dose of 20 mg followed by incremental doses of 20 to 80 mg every 10 minutes until the target blood pressure is achieved or the dose reaches a maximum of 300 mg. An alternative regimen is a continuous infusion starting at 1 to 2 mg/min with up-titration to achieve a desired blood pressure endpoint. Adverse effects of labetalol include orthostatic hypotension, bronchospasm, heart failure, and significant bradycardia. Labetalol should be avoided in patients with sinus bradycardia or heart block greater than

the first degree.

Nicardipine

Nicardipine is a short-acting calcium channel antagonist that produces selective arteriolar dilation. Nicardipine decreases systemic vascular resistance, without producing reflex tachycardia, while maintaining or increasing cardiac output. IV nicardipine has a relatively rapid onset of action and an offset of action of approximately 30 minutes, making it easily titratable when treating hypertensive emergencies. An initial dose of 5 mg/h is recommended. Blood pressure control is achieved with incremental increases in the infusion rate by 2.5 mg/h (every 5-15 minutes) to a maximum rate of 15 mg/h. Once the target blood pressure is achieved, the infusion rate can be reduced to 3 mg/h and adjusted to maintain the desired endpoint. Nicardipine is metabolized by the liver into inactive metabolites. In patients with aortic stenosis, patients with cardiomyopathy receiving β-blockers, and patients with impaired hepatic function, nicardipine should be avoided or used with extreme caution. Studies comparing nicardipine to nitroprusside in the management of postoperative hypertension have shown similar efficacy. Nicardipine has been used successfully in pregnant patients with hypertensive emergencies and in neurological diseases requiring tight blood pressure control.

Nitroprusside

Sodium nitroprusside is the oldest IV drug administered for hypertensive emergencies. Nitroprusside is a potent balanced arterial and venous vasodilator that decreases both cardiac afterload and preload. It has a rapid onset of action (2-3 minutes) and short serum half-life (1-2 minutes) and can be easily titrated. Nitroprusside is typically begun at 0.3 μg/kg/min and increased by 0.2 to 1.0 μg/kg/min every 3 to 5 minutes as needed until reading a maximum of 2 μg/kg/min. Because of its potent effects on blood pressure, the use of nitroprusside requires invasive hemodynamic monitoring (arterial line for continuous blood pressure monitoring). Nitroprusside has metabolites with potential toxicity (cyanide and thiocyanate). Cyanide is released nonenzymatically from nitroprusside and converted to thiocyanate by the liver, and thiocyanate is excreted by the kidneys. The total cumulative dose of nitroprusside, liver failure, and renal dysfunction increase the risk for toxicity. Cyanide toxicity is associated with lactic acidosis, mental status changes, and hypotension. Signs of thiocyanate toxicity include delirium, headaches, nausea, abdominal pain, and muscular spasms. To reduce possible toxicity, the duration

of treatment with nitroprusside should be limited and the maintenance rate of infusion should not exceed 2 μg/kg/min. In patients requiring higher doses of nitroprusside, an infusion of thiosulfate or hydroxocobalamin is recommended to decrease risk of toxicity. Methemoglobinemia is another rare complication in patients receiving more than 10 mg/kg of sodium nitroprusside. Despite concerns of potential toxicity, nitroprusside remains a viable alternative for the treatment of hypertensive emergencies.

Other Agents

Several other agents have been used to treat hypertensive crises. Nitroglycerin directly interacts with nitrate receptors, producing predominantly venous dilation. Because of its favorable effects on coronary perfusion and its ability to reduce preload, nitroglycerin is well suited for treating hypertensive emergencies associated with myocardial ischemia or acute left ventricular failure. Enalaprilat is an angiotensin-converting enzyme inhibitor that can be administered intravenously. It is especially useful in hypertensive emergencies associated with scleroderma crises. Phentolamine is an α-adrenergic blocking agent that may be used for the management of catecholamine-induced hypertensive emergencies, such as pheochromocytoma.

SPECIFIC CLINICAL CONSIDERATIONS

Acute Aortic Dissection

Acute aortic dissection, a life-threatening complication of hypertension, is caused by a tear in the intima of the aorta. This tear is then propagated by the aortic pulse wave, which is dependent on myocardial contractility, heart rate, and blood pressure. The presenting symptom is usually severe, sharp chest pain of abrupt onset. The chest radiograph may reveal a widened mediastinum, but the diagnosis is best made with a contrast-enhanced computed tomography scan or transesophageal echocardiography. Aortic dissections are classified as type A (proximal to the left subclavian artery, involving the ascending aorta) or type B (distal to the left subclavian artery, involving the descending aorta). The goal of treatment is rapid reduction of the pulsatile wave and aortic stress. Both MAP and cardiac output must be controlled to achieve this goal and prevent further propagation of the dissection in the aorta. In patients with aortic dissection, the MAP and heart rate should be reduced to normal values as quickly as possible. A combination of a vasodilator (nitroprusside, nicardipine, fenoldopam) with a β-

blocker (esmolol, metoprolol) is recommended. All patients with aortic dissection need emergent cardiovascular surgical evaluation. Type A dissections usually require emergent surgery to prevent serious complications such as acute aortic insufficiency, hemopericardium, and cardiac tamponade. Type B dissections are often managed medically. Indications for surgery in type B dissections include complications such as leak, rupture, or impaired flow to vital organs.

Cerebrovascular Accidents

Hypertension is common after both ischemic and hemorrhagic strokes. Extreme elevations in blood pressure have been associated with poor outcomes after ischemic and hemorrhagic strokes, raising the concern for reinfarction, cerebral edema, increased hemorrhage size, and hemorrhagic transformation of ischemic lesions. After an acute stroke, the cerebral vasculature's ability to autoregulate blood flow is impaired. During this time period, flow to the brain is highly dependent on MAP. Even modest reductions in blood pressure can compromise blood flow to the brain during this period, increasing the potential for secondary neurological damage. Optimal treatment of blood pressure during stroke remains controversial. Current guidelines recommend withholding therapy for hypertension in the acute phase of ischemic strokes except in patients who will receive thrombolysis, patients with evidence of concomitant acute end-organ damage, or those with excessive elevations in blood pressure (systolic blood pressure >220 mm Hg or diastolic blood pressure >120 mm Hg). For hemorrhagic strokes, current recommendations are to maintain a MAP of 130 mm Hg or lower in patients with a history of hypertension and 100 mm Hg or lower in patients who have undergone craniotomy. Current guidelines are summarized in **Table 2**.

Table 2. Guidelines for Treatment of Hypertension in Cerebrovascular

Clinical Parameter	Treatment
Ischemic stroke	
Patients not eligible for thrombolysis	
SBP <220 or DBP <120 mm Hg	No treatment
SBP >220 or DBP 121-140 mm Hg	Labetalol or nicardipine to 10%-15% reduction
DBP >140 mm Hg	Nitroprusside to 10%-15% reduction More labetalol or nicardipine
Patients eligible for thrombolysis	

Prior to thrombolytics	
SBP >185 or DBP >110 mm Hg	Labetalol or nitropaste
During or after thrombolytics	
SBP 180-230 or DBP 105-120 mm Hg	Labetalol
SPB >230 or DBP 121-140 mm Hg	Labetalol or nicardipine
DBP >140 mm Hg	Nitroprusside
Hemorrhagic stroke	
SBP <180 and DBP <105 mm Hg MAP <130 mm Hg	No treatment
SBP 180-230 or DBP 105-140 mm Hg MAP 130-160 mm Hg	Labetalol, esmolol, nicardipine, enalaprilat
SBP >230 or DBP >140 mm Hg MAP >160 mm Hg	Nitroprusside Nicardipine ± labetalol

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Hypertensive Encephalopathy

Hypertensive encephalopathy is characterized by headache, visual disturbances, confusion, and focal or generalized weakness. When the MAP exceeds the upper limits of cerebral blood flow autoregulation, endothelial damage with extravasation of plasma proteins can lead to cerebral edema. If untreated, hypertensive encephalopathy can lead to coma and death. Magnetic resonance imaging has demonstrated a classic radiographic appearance, referred to as *posterior reversible encephalopathy syndrome*. The differential diagnosis of hypertensive encephalopathy involves several neurological syndromes including stroke, subarachnoid hemorrhage, subdural or epidural hematoma, central nervous system vasculitis, seizures, and withdrawal syndromes. Treatment should be instituted immediately. A hallmark of hypertensive encephalopathy is improvement of the symptoms with blood pressure control. Caution should be taken not to worsen neurological symptoms from hypoperfusion caused by excessive lowering of the blood pressure. Medications suitable for treating hypertensive encephalopathy include nitroprusside, nicardipine, labetalol, and fenoldopam.

Pregnancy

Hypertension is a common complication of pregnancy and is responsible for

18% of maternal deaths in the United States. The spectrum of disease varies from mild increases in blood pressure to severe pregnancy-related syndromes with hypertensive emergency such as preeclampsia and eclampsia. Hypertension in pregnancy is defined as a systolic blood pressure 140 mm Hg or greater or a diastolic blood pressure 90 mm Hg or greater. Preeclampsia is a pregnancy-specific condition defined by new-onset hypertension, proteinuria (>300 mg per 24 hours), and pathological edema during gestation. Eclampsia is defined by the development of seizures or coma in a pregnant patient with preeclampsia. The challenge in pregnant patients with hypertensive crises is to lower the blood pressure in order to prevent maternal end-organ damage while minimizing acute changes in placental perfusion that could endanger the well-being of the fetus. Treatment of severe preeclampsia and eclampsia includes delivery of the fetus, administration of magnesium sulfate for prevention and treatment of seizures, and appropriate blood pressure control. The goal is to reduce the diastolic blood pressure to 100 mm Hg or the MAP by 20%. Historically, hydralazine has been preferred in pregnant patients for its safety profile from a fetal perspective; however, recent data suggest that it may not be the most effective or safe agent for this patient population. For pregnant patients who need acute lowering of blood pressure, labetalol and nicardipine are effective options. Nitroprusside is reserved for refractory cases because of concerns for potential fetal cyanide toxicity. Angiotensin-converting enzyme inhibitors such as enalaprilat are contraindicated in the second and third trimesters because of increases in fetal and neonatal morbidity and mortality.

SUMMARY

Hypertensive crises are classified as hypertensive emergencies and hypertensive urgencies. The presence of acute end-organ damage defines hypertensive emergencies and determines the therapeutic approach to lowering blood pressure. Patients with a hypertensive emergency require prompt reduction of elevated blood pressure to safe levels in order to prevent ongoing end-organ damage. Patients with a hypertensive emergency should be treated with IV medications in an ICU. Patients with elevated blood pressure without evidence of acute end-organ damage have a hypertensive urgency. In these cases, rapid reduction with IV medications is not indicated. Patients with a hypertensive urgency may be treated with oral medications with a goal to reduce blood pressure to safe levels over the following 24 to 48 hours.

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CHAPTER 15

Anaphylaxis

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Key words: anaphylactic shock, anaphylaxis, epinephrine, allergy

The definition of anaphylaxis has gone through several revisions and has been modified many times since its origin in 1901. Currently, *anaphylaxis* can be defined as a sudden-onset, severe, life-threatening, generalized or systemic, allergic or hypersensitivity reaction. In 2003, the World Allergy Organization suggested that the term *anaphylactoid* be abandoned and that all reactions of this type be called *anaphylactic episodes*, regardless of the involved mechanism. Furthermore, the organization recommended that these episodes be divided into the categories *immunological* and *nonimmunological*. Immunological episodes were to be subcategorized as mediated by immunoglobulin E (IgE) or not mediated by IgE. However, given the difficulties with standardizing definitions worldwide, the term *anaphylactoid* is still in use. *Idiopathic anaphylaxis* does not fit the above definitions and is placed in a separate category. Based on the International Consensus in Anaphylaxis, published in 2014, it is important to highlight that the word *shock* is not included in the definition, because shock is not necessarily present in patients with this reaction. Despite this, the term *anaphylactic shock* remains in common use due to the severity of anaphylactic reactions.

Exposure to environmental allergens and pollutants has resulted in an increase in the prevalence of allergic diseases worldwide. Numerous related international organizations including the World Allergy Organization promote awareness and develop evidence-based guidelines for prevention, diagnosis, and management of anaphylaxis. The reader is referred to those guidelines for more comprehensive information, as the goal of this chapter is to summarize key elements of anaphylactic disease for the critical care arena.

EPIDEMIOLOGICAL CHARACTERISTICS

Recent surveys estimate the lifetime risk of anaphylaxis in the general population in the United States at 1.6% to 5%. A large number of anaphylactic reactions are believed to be underdiagnosed; however, investigators worldwide have stated that the number of hospital admissions secondary to such allergic reactions have been on the rise in the last several years.

Despite the increase in hospital admissions, the number of fatalities related to anaphylaxis remains unchanged. When fatalities occur, they tend to be in elderly patients and most often a result of drugs (58.8%), unspecified triggers (19.3%), venoms (15.2%), or foods (6.7%). Old age combined with both cardiovascular disease and chronic obstructive pulmonary disease is an important risk factor for fatality.

Food remains the overall most common cause of anaphylaxis, with peanuts, tree nuts, fish, shellfish, and cow's milk being the most frequent triggers. Food-induced anaphylaxis occurs more often in children ages 0 to 4 years.

In adults, medications that are most likely to trigger anaphylaxis include antibiotics (most commonly a β-lactam), nonsteroidal anti-inflammatory drugs, and neuromuscular blocking agents. The combination of β-blockers and angiotensin-converting enzyme (ACE) inhibitors has been shown to increase mast cell histamine release. ACE inhibitors are considered to be a cofactor and, when combined with other agents, can trigger anaphylaxis. Reactions occurring within 1 hour are typically IgE mediated. Unfortunately, skin testing is of limited value for confirming allergy to medications, but it is validated for β-lactam antibiotics. In the United States it was reported that a history of penicillin allergy is associated with increased hospital length of stay, hospital cost, use of broad-spectrum antibiotics, and prevalence of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE) infections. Other drugs associated with anaphylaxis are omalizumab, sugammadex, chlorhexidine, and iodinated radiocontrast. Gadolinium-based contrast is often recommended for patients with a history of radiocontrast material–induced anaphylaxis. However, despite pretreatment with corticosteroids and antihistamines, anaphylaxis can still be triggered by gadolinium-based contrast in some patients.

Other causes of anaphylaxis are rare. Insect stings account for anaphylaxis in 3% of adult cases and 1% of children, most commonly by *Hymenoptera* venom. Of note, it is recommended that any individual with an anaphylactic response to a

hymenoptera sting should undergo a baseline serum tryptase measurement, as they are at risk of having undiagnosed systemic mastocytosis. Cofactor triggers such as ingestion of gluten or a combination of gluten, acetylsalicylic acid, and alcohol often play a role in exercise-induced anaphylaxis. Widespread use of latex-free products has led to a reduction in latex-induced allergic reactions in the United States, even in spina bifida patients and healthcare workers. Allergen immunotherapy injections are implicated in triggering anaphylaxis in 0.25% to 1.3% of cases. Systemic mastocytosis predisposes individuals to severe life-threatening anaphylaxis of all causes. Idiopathic anaphylaxis still contributes to a significant number of cases with unidentified triggers, and this diagnosis is only established when extensive history, skin tests, and measurement of allergen-specific IgE levels are not able to reveal a causative agent. **Table 1** summarizes the causes of anaphylaxis.

The case fatality rate of anaphylaxis is reported as less than 1% in most studies. Mortality increases in patients with preexisting or poorly controlled asthma. Airway compromise and cardiovascular collapse are typically the primary causes of death.

Table 1. Causes of Anaphylaxis

Food
Nuts (peanut, walnut, almond, brazil, hazel) Milk, fish, shellfish, chickpea, crustacean, banana, snail, grape, strawberry, red meat
Insect
Hymenoptera venom *Apidae* family (honeybees) *Vespidae* family (yellow jackets, hornets, wasps) *Formicidae* family (fire ants)
Drugs
Antibiotics (penicillin, cephalosporin, amphotericin, ciprofloxacin, vancomycin) Nonsteroidal anti-inflammatory drugs Neuromuscular blocker (atracurium, vecuronium, suxamethonium) Sugammadex Acetylsalicylic acid (ASA) Chlorhexidine Angiotensin-converting enzyme (ACE) inhibitors Protamine Acetazolamide Vitamin K
Other
Latex

Contrast media (iodinated, technetium, fluorescein, gadolinium)
Seminal fluid
Allergen immunotherapy (AIT)
Physical factors (exercise, cold, heat)

PATHOPHYSIOLOGICAL CHARACTERISTICS

In most cases, anaphylaxis occurs after the activation of mast cells and basophils through a mechanism that involves IgE and its high-affinity receptors (FceRI). Once an antigen binds to IgE, these FceRI receptors aggregate and initiate the signaling cascade. Specific sequences of the FceRI receptor are phosphorylated and activated, serving as high-affinity docking sites for a number of proteins that, in a sequential activation process, culminate with release of calcium and activation of protein kinase C leading to mast cell degranulation. Mast cells and/or basophils have secretory granules that release mediators such as histamine, tryptase, carboxypeptidase A, and proteoglycans. As the cascade continues, activation of phospholipase A_2, cyclooxygenase, and lipoxygenase takes place, and production of arachidonic acid metabolites (prostaglandins, leukotrienes, and platelet-activating factor) occurs. Tumor necrosis factor α (TNF-α) is released in the early and late phases. Clinicians need to understand the association between genetic predisposition and the variability of mast cell degranulation and anaphylactic responses from one patient to another. This is due to the critical role of tyrosine kinases (activated proteins in the signaling cascade) in positive and negative regulation of the mast cell activation process.

Histamine causes vasodilation and increased vascular permeability, tachycardia, cardiac contraction, and glandular secretion. Prostaglandin D_2 promotes bronchoconstriction, pulmonary and coronary vasoconstriction, and peripheral vasodilation. Leukotrienes account for bronchoconstriction, increased vascular permeability, and airway remodeling. Platelet activating factor contributes to bronchoconstriction and vascular permeability. TNF-α activates neutrophils, recruits other cells, and facilitates chemokine synthesis. All these physiological effects become synergistic and contribute to the pathophysiological process of anaphylaxis, which manifests clinically as urticaria and angioedema, bronchospasm, hypotension, syncope, other cardiovascular symptoms, nausea, cramping, and other gastrointestinal symptoms. An emerging mediator, called S1P, is thought to contribute to anaphylaxis with both an autocrine and paracrine mechanism, but more research is needed to establish its full role.

The above mediators cause hypotension via activation of nitric oxide synthase

and increased production of nitric oxide. Nitric oxide stimulates guanylyl cyclase and subsequently cyclic guanosine monophosphate (cGMP), thereby causing potent vasodilation by vascular smooth muscle relaxation.

Alternative mechanisms are hypothesized for cases in which anaphylaxis occurs without evidence of IgE involvement. Complement anaphylatoxin activation, neuropeptide release, immune complex generation, cytotoxicity, and T-cell activation, or a combination of these, are examples of these potential mechanisms. Overall, the pathophysiological process of anaphylaxis continues to be a challenging research topic that needs ongoing investigation, especially regarding reactions that are not mediated by IgE.

DIAGNOSIS

The diagnosis of anaphylactic reaction is clinical, obtained in the majority of cases by history, focusing on time of the event, exposure to possible trigger, time between exposure and development of symptoms, and evolution of the symptoms over the course of time. Other facts that may help in the history are activity at the time of event, location of the event, exposure to heat or cold during the event, and relation to menstrual cycle in females.

Because of a range of different possible signs and symptoms and a lack of a consistent clinical manifestation, the diagnosis of anaphylaxis may not be easy to establish. As a consequence, a single set of criteria for its diagnosis will not identity every single case; combinations of signs and symptoms make the diagnosis more likely.

Anaphylaxis is likely the diagnosis when the event is of sudden onset with rapid progression of symptoms (minutes to hours); promotes life-threatening airway, breathing, and/or circulation problems; and results in skin and/or mucosal changes (flushing, urticaria, angioedema). Of note, skin or mucosal changes alone are not a sign of an anaphylactic reaction, even though they are its most frequently seen signs and occur in 60% to 90% of cases. A major decrease in blood pressure after exposure to a known allergen, without skin changes, will suffice for a diagnosis of anaphylaxis. Other unusual presentations have been reported, such as syncope alone, without further signs or symptoms. Gastrointestinal disturbances including vomiting, abdominal pain, and incontinence may also be present (**Table 2**).

Table 2. Signs and Symptoms of Anaphylaxis

Skin
Urticaria Angioedema of skin or mucosa Flushing Pruritus without rash Pilar erection Conjunctival itching, redness, tearing, and/or swelling
Respiratory
Dyspnea Wheezing Cough Angioedema (upper airway—throat tightness/itching, dysphonia, hoarseness, stridor) Rhinitis Chest tightness Cyanosis Respiratory arrest
Cardiovascular
Hypotension Syncope Diaphoresis Chest pain Palpitations, tachycardia, arrhythmias Shock Cardiac arrest
Abdominal
Nausea Vomiting Diarrhea Abdominal pain Urinary or fecal incontinence
Others
Headache Dizziness Confusion Altered mental state or behavior Tunneled vision Sense of impending doom Uneasiness

Given the challenges in diagnosing anaphylaxis, a thorough assessment should include a comprehensive list of differential diagnoses. The hypothesis should

entail vasovagal reactions as well as flushing syndromes including medication-induced flushing (eg, niacin, nicotine, ACE inhibitors, alcohol), carcinoid syndrome, mastocytosis, vasointestinal polypeptide tumors, and medullary carcinoma of the thyroid. Nonorganic causes include panic attacks, Munchausen stridor, and vocal cord dysfunction syndrome. Other entities that can mimic anaphylaxis are pheochromocytoma, red man syndrome, capillary leak syndrome, and hereditary angioedema (**Table 3**).

Table 3. Differential Diagnosis of Anaphylaxis

Vasovagal Reactions
Carcinoid Vasointestinal polypeptide tumors Mastocytosis and mast cell activating syndrome Medullary carcinoma of the thyroid Monosodium glutamate Scombroidosis (from eating spoiled fish)
Nonorganic Disease
Panic attacks Munchausen stridor (factitious anaphylaxis) Vocal cord dysfunction syndrome Prevarication anaphylaxis
Other
Hereditary angioedema with rash Paradoxical pheochromocytoma Red man syndrome

Suspicion of anaphylaxis is based on clinical symptoms and the diagnosis needs to be established quickly due to its life-threatening potential, so laboratory investigation plays only a limited initial role. The usefulness of laboratory testing is restricted to the confirmation of the clinical diagnosis after management has taken place. Determinations of plasma histamine and tryptase are the mainstays of laboratory testing in anaphylaxis. Prostaglandin assays can be of value as confirmatory tests. Finally, α-gal, an oligosaccharide, has been implicated as a possible culprit in cases of anaphylaxis of unknown cause, and a test is currently available to detect serum specific IgE anti-α-gal.

Histamine levels, when elevated (42%-97% cases), remain so for only 30 to 60 minutes after development of presenting symptoms, so tryptase levels are most often tested instead. High levels of histamine are associated with urticaria,

extensive erythema, wheezing, and abdominal symptoms.

Elevated tryptase levels can be detected within 15 minutes, peak in 60 to 90 minutes, and remain elevated for up to 5 hours after the anaphylactic episode. Levels of 15.7 μg/L or higher are highly predictive of an IgE-mediated reaction. Other conditions that can elevate tryptase levels are mastocytosis, myelocytic leukemia, hypereosinophilic syndrome, myelodysplastic syndrome, end-stage renal disease, and C1 esterase deficiency associated with non-Hodgkin lymphoma. In those scenarios, an elevation 1.2 times or more the baseline indicates likelihood of mast cell activation. Interestingly, in food-induced anaphylaxis, tryptase levels are typically within normal range, again highlighting that the anaphylaxis is a clinical diagnosis without an absolute confirmatory laboratory test.

MANAGEMENT

Acute management starts with the assessment of the patient's airway, breathing, and circulation as well as elimination of the causative agent, if identified. Vital signs should be continuously monitored, supplemental oxygen provided for goal SpO_2 higher than 90%, large-bore IV access obtained, and IV fluid administration with normal saline initiated. Data do not support the use of either albumin or hypertonic saline instead of normal saline. Prompt assessment of airway patency should be performed, and endotracheal intubation should proceed if there are any anatomical signs of airway compromise. Delaying this step may result in fatal complete airway obstruction. Delayed administration of epinephrine is associated with an increased number of hospital admissions and fatalities. Several reasons have been implicated in the source of delay, such as mild symptoms, food-associated reaction, patient refusal, or perceived contraindications including pregnancy, older age, or cardiovascular disease. The bottom line is that there are no absolute contraindications to epinephrine in anaphylaxis. If wheezing is present, a selective bronchodilator such as albuterol should be administered, especially if wheezing persists after the initial therapy with epinephrine.

The 2015 update of the World Allergy Organization's anaphylaxis guidelines states that epinephrine is the first-choice medication for anaphylaxis because it is the only intervention that decreases hospitalization and mortality. The combined α- and β-agonist effects of epinephrine are beneficial. The α_1 stimulation causes significant vasoconstriction, preventing and relieving airway edema,

hypotension, and shock. The β_1 chronotropic and inotropic actions increase the heart rate and cardiac contractions, improving hemodynamics. The β_2 effects result in bronchodilation and decreased mediator release, preventing escalation of the reaction. In adults, a dose of 0.2 to 0.5 mg epinephrine 1:1,000 (1 mg/mL) given intramuscularly (IM) (lateral thigh) resulted in higher peak concentrations than the SQ route. Injection can be repeated every 5 to 10 minutes if necessary. Evidence supports the safety of the IM route compared with the IV route: 1% vs 13% adverse events reported with IM vs IV, respectively. However, controversy exists regarding the optimal dosing and route for treatment of anaphylaxis that occurs in critical care settings due to concerns regarding potential limitations of regional blood flow in ICU patients and possible side effects of epinephrine. IV epinephrine may be preferred in patients who do not respond to IM doses or for those with profound signs and symptoms suggesting impending cardiac arrest. If the IV route is chosen, it should be used with caution, in a controlled setting with continuous monitoring, such as the ICU, emergency department, or operating room setting. The IV route using doses of 10 to 100 μg in escalating doses every 2 minutes and proceeding to a continuous infusion is commonly the first choice as these patients will typically have IV access and continuous cardiac monitoring in place. In prolonged refractory cases, epinephrine can be given as an infusion at a rate of 1 to 10 μg/min, and dopamine and vasopressin may be adjuncts. Critically ill patients may have altered absorption from the IM route, justifying IV epinephrine administration with appropriate monitoring for adverse side effects. However, extreme caution must be taken to avoid injection of undiluted epinephrine or infusions mixed in haste with error in dilution. Due to these reasons, initial IM injection may be preferred even in the ICU setting. Of note, patients refractory to epinephrine or those who have been receiving β-blockers may not respond appropriately to epinephrine, and IV glucagon at a dose of 1 to 5 mg should be attempted, followed by an infusion (5-15 μg/min). Potential glucagon side effects are nausea, vomiting, hypokalemia, dizziness, and hyperglycemia. Epinephrine auto-injectors for IM administration are available in the United States in two doses: 0.15 mg and 0.3 mg. These devices are commonly prescribed in the outpatient or clinic setting for severe allergic and anaphylactic reactions and should be considered for any patients with newly diagnosed anaphylaxis due to a specific exposure.

Perioperative anaphylaxis has greater morbidity and mortality (ie, 1.4%-6%) than other forms of anaphylaxis and is an example of when IV epinephrine may be preferred by experienced physicians. Intraoperative anaphylaxis is thought to occur in up to 1 in 20,000 anesthetics. It is a serious complication that can

develop after the administration of neuromuscular blocking agents (atracurium, suxamethonium, rocuronium, vecuronium) or antibiotics (50% of cases in the United States), blood and blood products, dyes, chlorhexidine, protamine, hypnotic agents, narcotics, or latex. Individual risk factors associated with fatality are male gender, emergency setting, history of hypertension or other cardiovascular disease, ongoing β-blocker treatment, and obesity. Diagnosis is challenging in the operative setting due to the difficulty identifying the typical signs and symptoms in this patient population, the presence of other physiological variables related to anesthesia and surgery, the presence of drapes covering the patient, and the fact that the patient is unconscious. For patients with a history of anaphylaxis that are undergoing surgery, a baseline total serum tryptase may be useful to rule out clonal mast cell disorders or mastocytosis, since both increase risk of anaphylaxis. Additionally, in patients with a history of anaphylaxis who require surgery, clinicians should address the following issues: asthma should be well controlled, antibiotics and drugs with potential for histamine release should be infused very slowly, and risks and benefits of β-blockers and ACE inhibitors considered carefully as they may be detrimental if anaphylaxis develops. Of note, patients on chronic β-blockers for coronary artery disease are at risk of ischemia with withdrawal of β-blockade so these patients should continue these agents perioperatively. According to 2014 guidelines ACE inhibitors can be continued perioperatively, but this decision can be individualized based on indication, type of surgery, planned anesthetic, and patient risk factors.

Given the severity of this perioperative scenario, many institutions have created their own checklists for the management of anaphylaxis. For example, the Stanford Anesthesia Cognitive Aid Group's Emergency Manual: Cognitive aids for perioperative critical events, recommends pausing the surgery, discontinuing volatile agents, switching the F_{IO_2} to 1.0 with high flow, and administering IV epinephrine 10 to 100 μg every 2 minutes until clinical improvement. The manual suggests adding vasopressin 2 to 4 units IV in cases of refractory hypotension and monitoring the patient for at least 24 hours post recovery. Use of an infusion or dilution of epinephrine to 10 μg/mL is recommended and must be done carefully to achieve accuracy and safety. After an episode of intraoperative anaphylaxis, a search should be undertaken to discover the causative agent and the patient should be warned regarding potential future episodes. Determination of the causative agent is complicated due to number of medications given in a short time window.

Second-line medications for the treatment of anaphylaxis are antihistamines (both H_1 and H_2 blockers) and glucocorticoids. The main difference between these drugs and epinephrine is that the second-line medications do not relieve upper or lower airway obstruction, hypotension, or shock and are not lifesaving; therefore, these agents should not be used as a first or sole option. H_2-antihistamines are thought to have a synergistic effect when associated with H_1-antihistamines in the setting of allergic reactions. Of note, most antihistamine studies were done in patients with skin symptoms rather than respiratory or cardiovascular symptoms. In addition, none of the patients had a diagnosis of anaphylaxis. Glucocorticoids have minimal effects on initial symptoms and signs of anaphylaxis. Their use is supported for the prevention of biphasic episodes or in the event of prolonged reactions. Hydrocortisone 250 to 500 mg IV and methylprednisolone 80 to 125 mg IV are equally viable options (**Table 4**). Current data suggest that routine prolonged monitoring is not necessary for patients whose anaphylaxis symptoms have resolved and that the duration of observation should be individualized according to the clinical characteristics and severity of each specific episode. Experts recommend at least 6 to 8 hours of monitoring after stabilization.

Table 4. Anaphylaxis Treatment

Immediate
Remove allergen, if possible.
Assess airway, breathing, circulation, and mentation.
Call for help and start cardiopulmonary resuscitation/Advanced Cardiac Life Support protocol if cardiac arrest occurs.
Administer epinephrine 0.3-0.5 mg IM in the vastus lateralis.
Get help.
Place patient in recumbent position, left lateral decubitus if pregnant.
Administer supplemental oxygen; monitor pulse oximetry.
Repeat epinephrine IM every 5-15 min for up to 3 injections.
Establish IV access and begin fluid replacement; push fluids for hypotension, 5-10 mL/kg, up to several liters in the first hour.
Administer epinephrine 10-100 μg IV every 2 min if patient in the ICU, operating room, or emergency department.
Additional
Administer albuterol, 2.5-5 mg in 3-mL nebulizer; may repeat every 15 min.
Administer glucagon, 1-5 mg IV over 5 min for patients receiving β-blockers who do not respond to epinephrine.
Administer epinephrine infusion, 1-10 μg/min (concentration of 1 μg/mL).
Refractory
Consider intraosseous access in refractory anaphylaxis when IV access is not readily available.

Secure airway.
Consider adding dopamine infusion, 5-20 μg/kg/min.
Consider glucagon (even if patient not receiving β-blockers) or methylene blue if no response to above interventions.
Administer H_1 antihistamine, 25-50 mg IV (diphenhydramine).
Administer corticosteroids, 1-2 mg/kg up to 125 mg per dose, IV (methylprednisolone or equivalent).

Anaphylactic shock that is refractory to epinephrine and aggressive fluid resuscitation may benefit from alternative and temporary measures. Methylene blue has been used with success in anaphylaxis and septic shock refractory to other therapies. The mechanism of action is likely through inhibition of selective nitric oxide and cGMP, thereby preventing generalized vasodilation. Furthermore, for selected cases and where expertise is available, extracorporeal membrane oxygenation may be an option as a bridge to recovery in cases of cardiovascular collapse.

SUMMARY

Anaphylaxis is a life-threatening condition that demands quick and effective diagnosis and management. Given its unpredictable rate of escalation and resolution of symptoms, anaphylaxis requires prompt recognition and appropriate treatment by healthcare professionals. Several consensus guidelines have been published with the goal of optimizing recognition and care of patients with anaphylaxis. Epinephrine remains the keystone of treatment for acute episodes, as it has immediate clinical benefit and decreases hospital admissions. Intravenous epinephrine is likely to remain the preferred route of administration by critical care teams in the controlled ICU level environments, although practice guidelines consider the IM route to be the safest approach. Additional therapies may be instituted but should never replace or precede epinephrine.

Summary Points

- Immediate and aggressive management of suspected anaphylaxis is imperative.
- Epinephrine is the mainstay of therapy, and delayed administration is associated with increased fatalities and poorer outcomes.
- Episodes refractory to epinephrine or in patients receiving β-blocker therapy may respond to glucagon.

- Adjunctive treatment with antihistamines and glucocorticoids is not associated with improved survival but may reduce biphasic recurrence and prolonged symptoms.
- Tryptase levels may be useful as confirmatory tests as they peak 60 to 90 minutes after symptoms occur and decrease rapidly.
- Efforts to determine the causative agent are required to prevent future episodes.

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CHAPTER 16

Extracorporeal Membrane Oxygenation

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The illustrations were designed by Kim Chapman in the Department of Medical Media of the Clement J. Zablocki VAMC.

Key words: ECMO, circuit, cannula, cardiac failure, respiratory failure, ARDS

Since the first application of extracorporeal membrane oxygenation (ECMO) in 1970s, great advances have taken place in our understanding of the pathophysiological characteristics of diseases, in the development of advanced diagnostic technology, and in the application of novel therapeutic modalities.

Clinicians initially considered ECMO an appealing "rescue" modality, but early studies assessing morbidity, mortality, and neurological outcome were discouraging. Since that time, biochemical and biomechanical engineering has improved the profile of the oxygenators and the safety mechanism of the pumps, such that recovery from lung or heart failure is now more likely. More important, ECMO is no longer just a rescue therapy but is used earlier in treatment algorithms.

Advances in this technology in critical care as well as increased demands imposed by newer pandemics (eg, swine flu, or N1H1) obligate the intensive care physician to become familiar with the initiation, management, and weaning of ECMO. Best survival results are seen in high-volume ECMO centers and when the duration of mechanical ventilation prior to initiation of ECMO is less than 5 days.

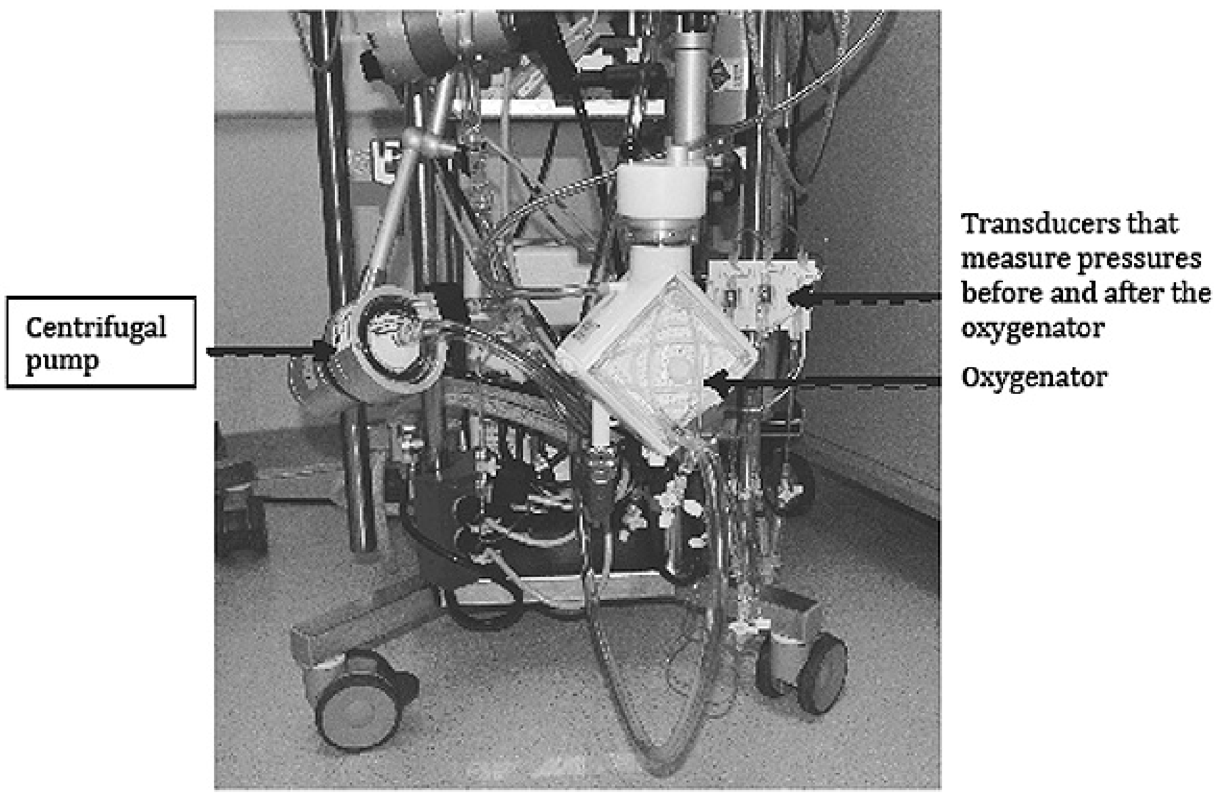
ECMO CIRCUIT

The ECMO circuit consists of a drainage cannula that receives the deoxygenated blood, a pump (centrifugal or roller), an oxygenator, a heat exchanger, and a

reinfusion cannula that returns the oxygenated blood to the circulation.

Roller pumps need a reservoir between the venous cannula and the pump and rely on gravity to fill the reservoir. The pump used in more modern circuits is a centrifugal one (**Figure 1**). The oxygenator consists of a silicone semipermeable membrane or hollow fiber. Silicone oxygenators are relatively nonthrombogenic. However, they are more resistant to blood flow and cannot be coated with heparin. Hollow fibers are quickly primed and can be coated with heparin.

Figure 1. Oxygenator, the centrifugal pump, and the transducers that measure the pressure before and after the oxygenator



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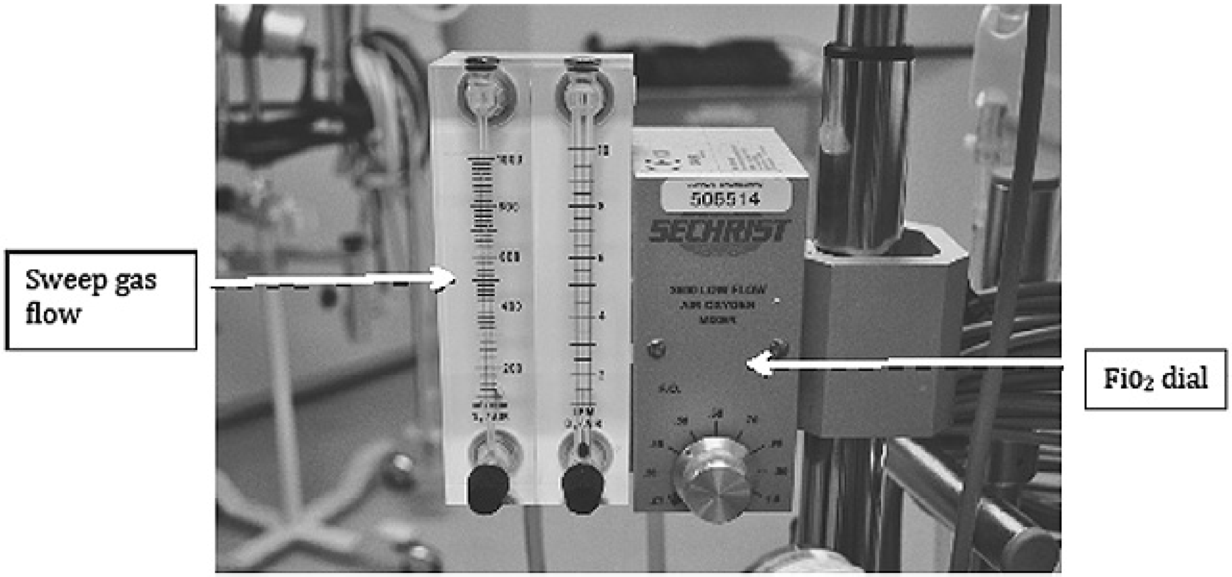
Fresh gas ("sweep gas") enters the gas side of the oxygenator membrane, which exchanges oxygen and carbon dioxide with the extracorporeal blood on the other side of the membrane. A blender mixes air with the oxygen and delivers this to the oxygenator (**Figure 2**). This fraction of delivered oxygen (Fdo_2) is not technically $F\textsc{io}_2$ because it is not inspired gas. Carbon dioxide is controlled by adjusting the flow rate of the sweep gas. Oxygenation is primarily controlled by the blood flow through the ECMO circuit.

Figure 2. The blender: The increase of the sweep gas flow allows more fresh gas to pass through the oxygenator, resulting in elimination of more carbon dioxide



The F_{IO_2} dial determines oxygenation.

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

The heat exchanger is often integrated within the oxygenator and, as its name implies, is used to either warm or cool the patient (**Figure 3**).

Figure 3. ECMO circuit

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

The drainage cannula receives blood from either the superior or the inferior vena cava (SVC or IVC). The largest cannula possible (23-29F) should be placed, as this cannula determines blood flow. Ultrasound of the vessel can aid in size determination. The centrifugal pump delivers flows up to 8 L/min at up to 4,000 revolutions per minute (RPM) and is reliable for up to 3 weeks (**Figure 4**). The flow through the circuit depends mainly on the inflow of blood into the system and the RPM set on the pump and less on the resistance of the outflow (cannula or vascular resistance).

Figure 4. The central control unit

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

Two types of ECMO are available: Venovenous (VV) is primarily used for respiratory failure, while venoarterial (VA) is used for cardiac failure.

INDICATIONS

Initiation criteria for VV ECMO are as follows:

1. Inadequate oxygenation: PaO_2:FIO_2 ratio less than 50 within the first 12 hours of respiratory failure or less than 100 if this deterioration of gas exchange occurred over several days. VV ECMO is indicated if this deterioration occurred despite optimization of conventional ventilator settings (including positive end-expiratory pressure, inspiratory-expiratory ratio, and tidal volumes), failure of attempts to induce diuresis, use of prone positioning, and administration of inhaled nitric oxide.
2. Inadequate ventilation: Hypercapnic respiratory failure with an arterial pH less than 7.20.
3. Excessive plateau pressures (ie, >45 cm H_2O).

Initiation criteria for VA-ECMO are as follows:

1. Cardiac arrest.
2. Refractory cardiogenic shock with increasing lactic acid, systolic blood pressure less than 90 mm Hg, and cardiac output less than 2.0 L/min despite

maximal inotropic therapy and intra-aortic balloon pump.

3. Failure to wean from cardiopulmonary bypass after cardiac surgery.
4. As a bridge to a ventricular assist device or bridge to cardiac transplantation.

GENERAL CONTRAINDICATIONS

Considerations for exclusion of ECMO include:

1. Severe neurological compromise
2. Contraindication to anticoagulation
3. Terminal disease
4. Multisystem organ failure
5. Mechanical ventilation for 2 weeks prior to ECMO
6. Age more than 70 years
7. End-stage lung disease
8. Patient not a candidate for transplant or ventricular assist device due to poor social support, severe aortic insufficiency, or preexisting renal failure

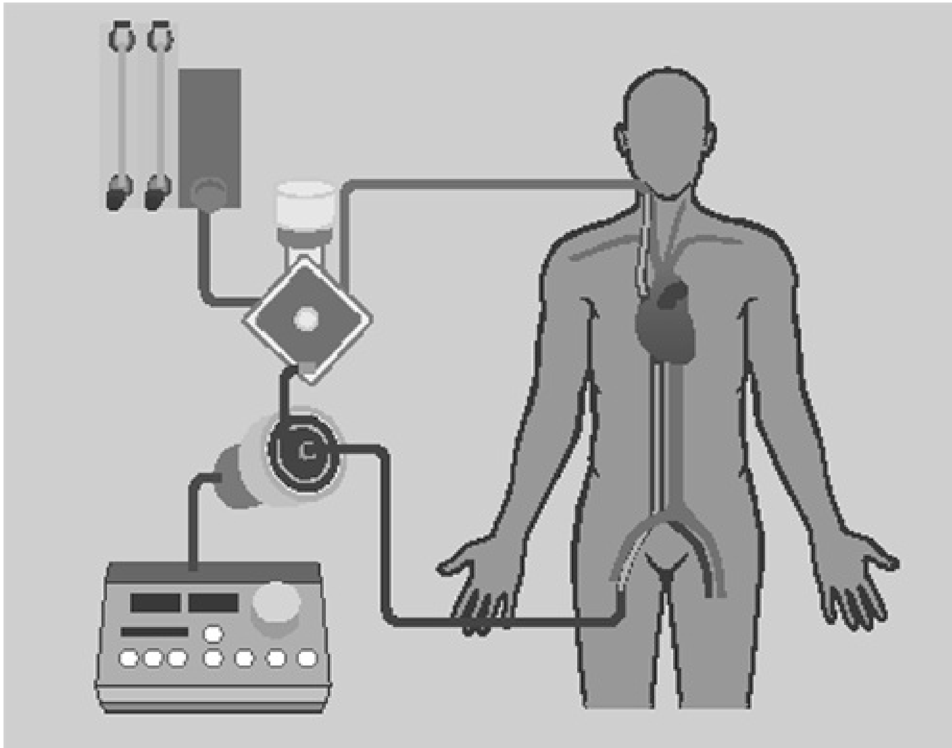
VENOVENOUS ECMO

VV ECMO is used for respiratory failure that does not improve with conventional mechanical ventilation. The most common indications are acute respiratory distress syndrome (ARDS), specifically attributable to H1N1 infection, and bridge to lung transplant (more common for patients with cystic fibrosis). Patients with irreversible respiratory failure and those deemed not to be transplant candidates should not be offered ECMO.

The oxygenated blood returns to the right atrium and flows through the lungs into the left ventricle (LV). VV ECMO provides only respiratory support, so the heart must be able to eject well enough. The oxygenation is mostly determined by the ECMO circuit flow.

Two types of cannulation are available for VV ECMO. With double-site cannulation, the drainage cannula is placed in the right femoral vein all the way in the IVC just below the diaphragm, and the reinfusion cannula is placed in the right internal jugular vein (**Figure 5**).

Figure 5. Double-site cannulation via right femoral vein and inferior vena cava (tip placed below the diaphragm)



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In single-site cannulation, a double-lumen cannula (eg, Avalon®, MAQUET Cardiovascular, Wayne, NJ) is placed in the right internal jugular vein. The distal port is placed into the IVC, where it receives the blood. The proximal port is used for the reinfusion of oxygenated blood into the right atrium and directs the flow toward the tricuspid valve (**Figures 6 and 7**). The correct orientation is achieved by the use of fluoroscopy or echocardiography, either transthoracic (TTE) or transesophageal (TEE).

Figure 6. Single-site cannulation via the right internal jugular vein

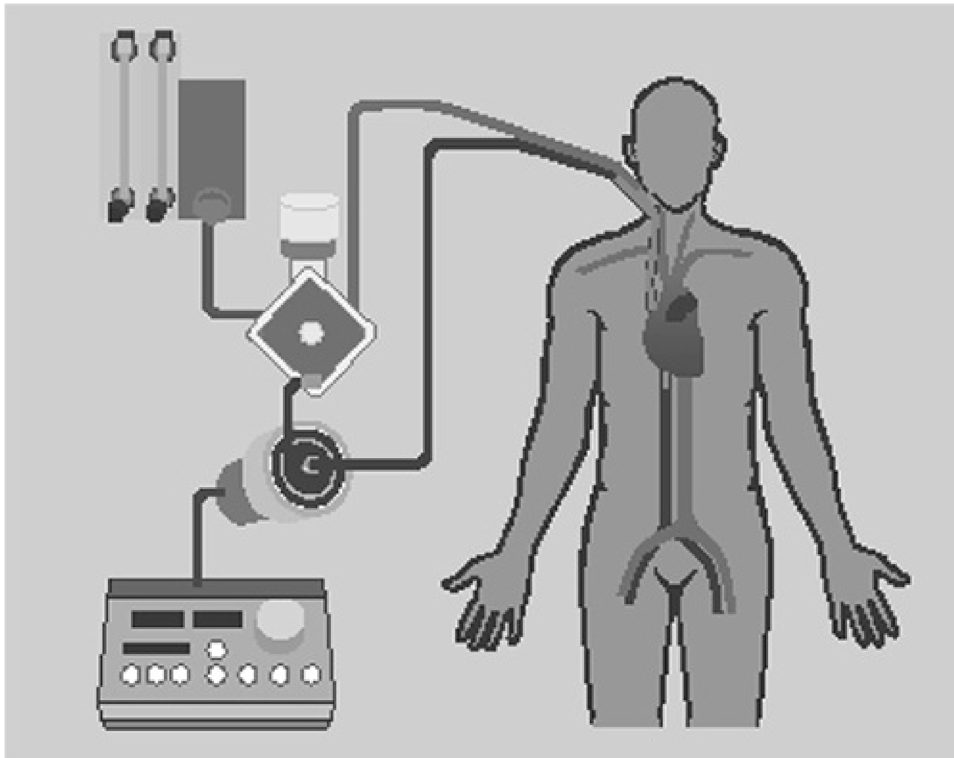

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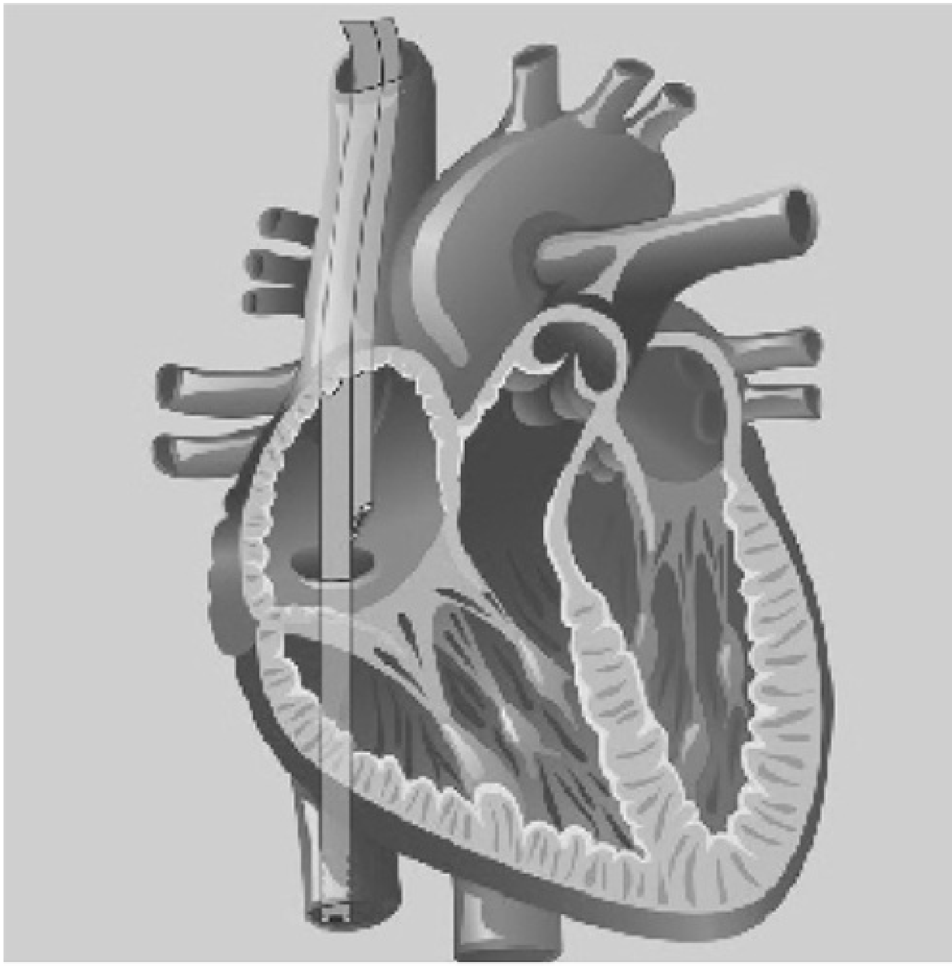
Figure 7. Single cannula with 2 lumens



The drainage lumen is positioned in the inferior vena cava and the reinfusion lumen in the right atrium, directing the oxygenated blood through the tricuspid valve.

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

VV ECMO for patients with ARDS allows for a lung-protective ventilation strategy with smaller tidal volumes, lower FIO_2, less barotrauma, and proven less inflammatory process in the alveolar bed.

The benefit of single-cannula VV ECMO is avoidance of femoral site access, reduction in recirculation, and enhanced patient mobility. Reduction in mechanical ventilation days especially benefits patients with respiratory failure who are awaiting lung transplantation. For these transplant candidates, mobilization and improvement in their physical condition can keep them on the transplant list while avoiding physical decompensation, thereby improving their postoperative outcome.

VV ECMO does not abolish the need for ventilation. The blood from the IVC is received by the circuit and oxygenated. A fraction of blood (mainly from the upper body) is still deoxygenated when it passes through the lungs. The remaining ability of the lungs to oxygenate and the underlying disease process are two of the primary factors that influence the choice of the mode of ventilation. For severe ARDS, the recommended ventilation strategy includes "ultraprotective" lung ventilation to reduce the risk of barotrauma, volutrauma, and oxygen toxicity. This strategy entails the following:

- Positive end-expiratory pressure greater than 10 cm H_2O (to reduce alveolar damage from atelectasis)
- F_{IO_2} 30% to 50% (to titrate Sp_{O_2} >85%)
- Plateau pressures 20 to 25 cm H_2O (to reduce alveolar stress trauma)
- Tidal volume 4 mL/kg (dry ideal body weight)
- Respiratory rate 10 breaths per minute

The Extracorporeal Life Support Organization (ELSO) recommends moderate to heavy sedation for the first 24 hours with pressure-controlled ventilation of 25/15 cm H_2O, inspiratory-expiratory ratio 2:1, rate 5, F_{IO_2} 50%, and slow decrease of the Pa_{CO_2} 10 to 20 mm Hg/h (by increasing the sweep flows). This gradual decrease is recommended to avoid a large gradient between the blood and intracellular pH, which takes some hours to equalize. In addition, the carotid arteries are maximally dilated from hypercarbia and the autoregulation curve has been shifted. Abrupt correction of the Pa_{CO_2} may potentially decrease the cerebral blood supply.

For the next 24 hours, as long as the patient remains hemodynamically stable and any infection is under control, the recommendations include gradual weaning of the Fd_{O_2} and of sedation. The final goal is to minimize sedation and resume spontaneous ventilation in addition to the pressure-controlled ventilation after the initial 48 hours.

For patients in severe hypercarbic respiratory failure, a slightly different mode of VV ECMO can be used. Extracorporeal CO_2 removal ($ECCO_2$-R) requires lower sweep flows and less blood flow through the circuit and can be achieved with significantly smaller cannulas and even with more peripheral cannulation.

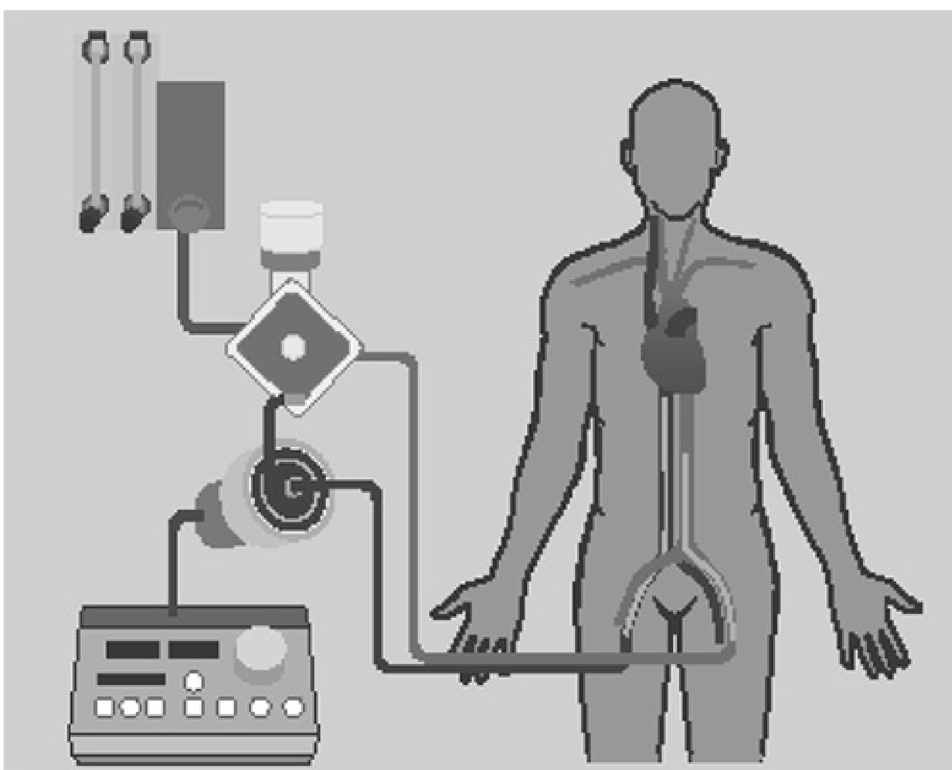
VENOARTERIAL ECMO

The indications for VA ECMO consist of cardiogenic shock, cardiac arrest, and severe pulmonary hypertension with acute failure of the right side of the heart as well as failure to wean from cardiopulmonary bypass. The list has expanded over the years with various indications and includes sepsis with high cardiac output heart failure, rewarming after environmental hypothermia involving cardiac depression or arrest, and other clinical situations of cardiogenic decompensation.

In VA ECMO, the deoxygenated blood is drained via the SVC or IVC, and the oxygenated blood is returned to the arterial system via the femoral or axillary artery, totally bypassing the heart and lungs. Thus, VA ECMO provides complete respiratory and cardiac support. For failure to wean from cardiopulmonary bypass a central cannulation technique is used whereby the drainage cannula is placed into the right atrium and the blood is turned to the ascending aorta.

The most common example of peripheral cannulation is bifemoral cannulation. The drainage cannula is placed in the femoral vein and the reinfusion cannula in the femoral artery (**Figure 8**).

Figure 8. VA ECMO with femoral vein and artery cannulations



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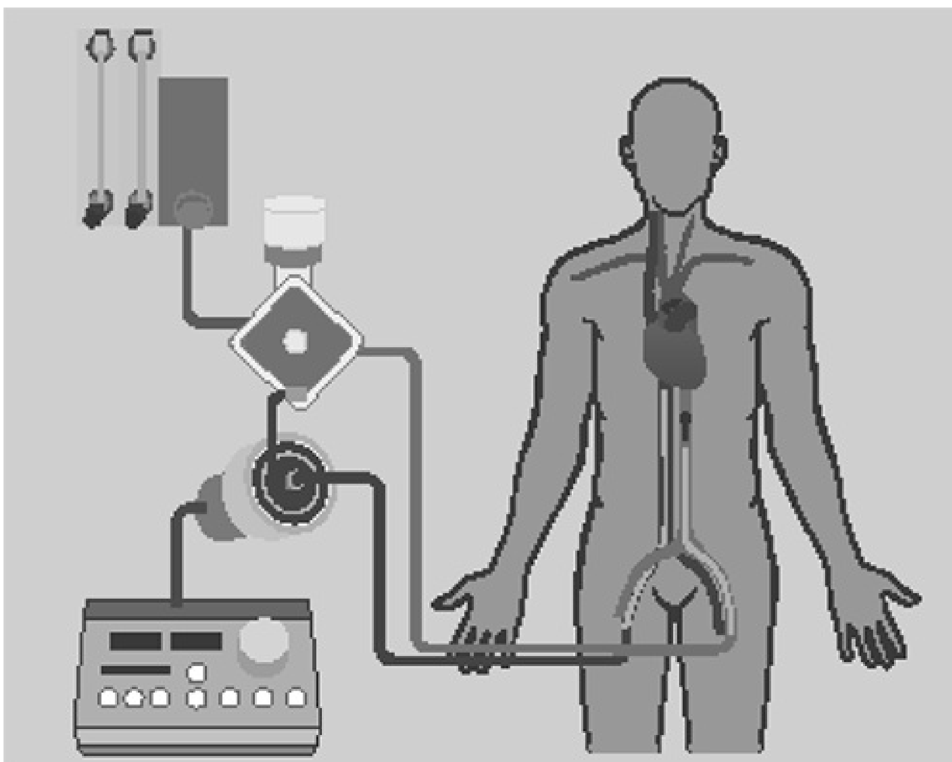
A proportion of the blood is received by ECMO and after being oxygenated is directed into the abdominal aorta (retrograde perfusion of the upper body). The rest of the blood flow passes through the lungs and is ejected into the ascending aorta. When the ventilation or oxygenation (diffusion capacity of the lungs) is impaired, the upper part of the body (cerebral and coronary circulation) receives mostly desaturated blood (**Figure 9**). Cardiac and cerebral hypoxia could go unrecognized if saturation is only measured in the lower limbs. This upper body desaturation is referred to as Harlequin syndrome.

Figure 9. VA ECMO with poor lung function and upper body desaturation (Harlequin syndrome)



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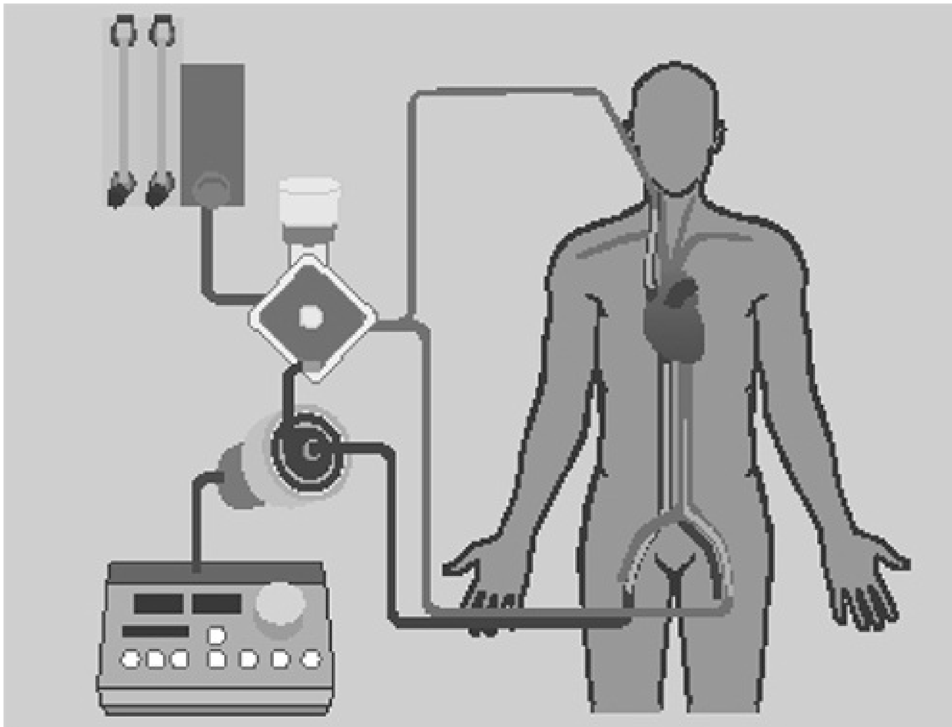
To improve the oxygen delivery to these two sensitive areas, the VA ECMO can be modified by adding a cannula in the right internal jugular vein that infuses oxygenated blood (Y connection with the arterial limb), creating a VA-V ECMO system (**Figure 10**). Oxygenated blood now flows through the native cardiac pathway, increasing the saturation of the blood reaching the upper part of the body.

Figure 10. VA-V ECMO with Y-connector to right internal jugular vein



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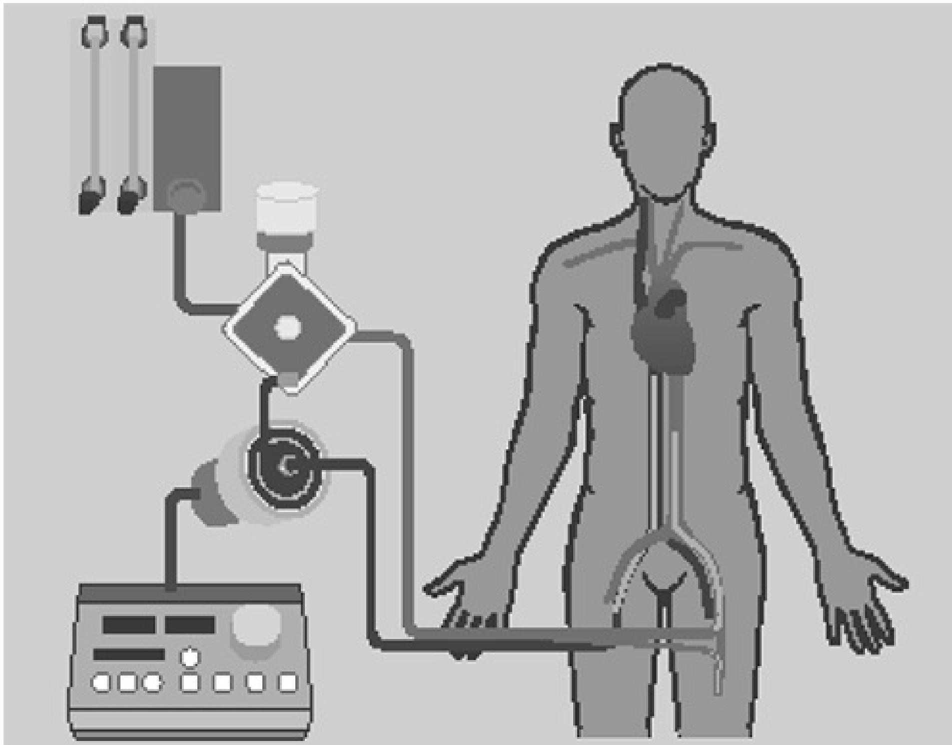
The ipsilateral lower extremity distal to the femoral arterial cannulation site is at risk for ischemic compromise and requires vigilant physical evaluation. An additional cannula placed distal to the femoral artery redirects a portion of the blood flow via this cannula to the leg (**Figure 11**). Alternatively, a cannula can be placed into the posterior tibial artery for retrograde flow to the lower extremity.

Figure 11. VA ECMO with cannula placed distally for leg perfusion



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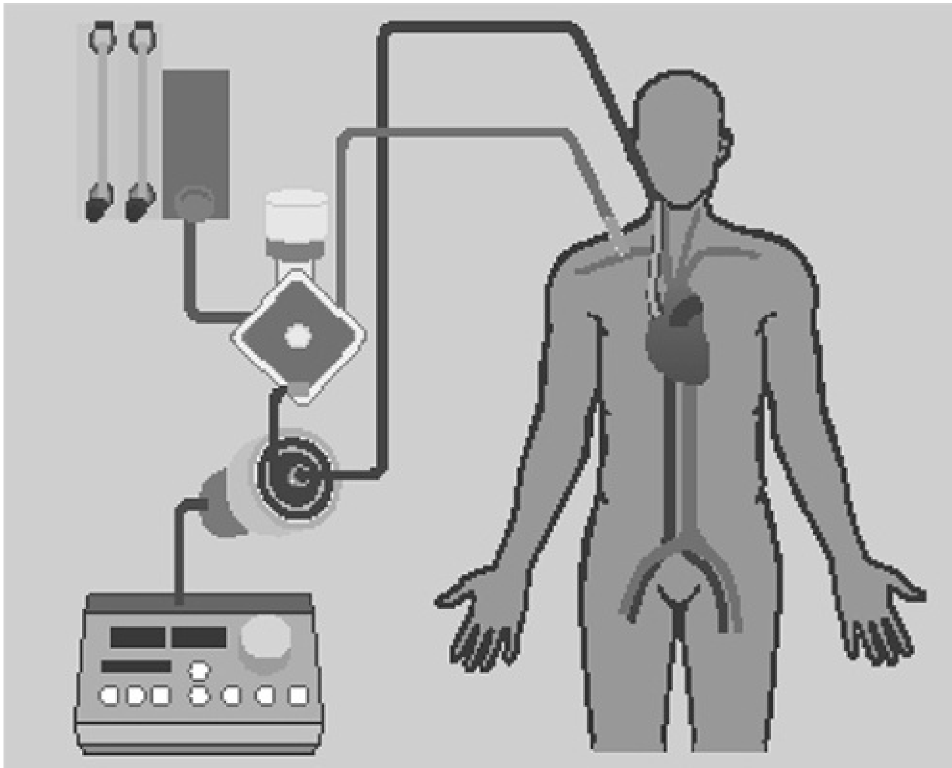
A more effective way to eliminate these issues is by using an artery of the upper body for reinfusion. An end-to-side graft to the subclavian artery (most commonly right) can be used as the efferent limb of the ECMO circuit with a right internal jugular cannula serving as the afferent limb. This technique is more favorable because it supplies the upper body with oxygenated blood, reduces the risk of infection, and eliminates the risk of vascular compromise of the leg while at the same time being more comfortable for the patient (**Figure 12**).

Figure 12. VA ECMO with insertion of the cannula into the right internal jugular vein and right subclavian artery



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For pediatric patients, peripheral cannulation most often consists of right internal jugular venous drainage and right common carotid reinfusion. This includes ligation of the carotid cephalad to the cannula insertion, which carries several consequences later in life (eg, stroke, poor neurological outcome, or inability to recannulate for ECMO from the same artery).

ECMO circuits have the ability to include ultrafiltration for patients who have acute renal failure or who require volume removal.

PREPARATION FOR AND INITIATION OF ECMO

It is helpful to review a checklist prior to insertion of cannulas (**Table 1**).

Table 1. ECMO Checklist

☐ Arterial line
☐ Central line
☐ Laboratory values Hemoglobin >10 mg/dL Platelets >50,000

☐ 4 U packed red blood cells available at bedside
☐ Heparin 1,000 U/mL at bedside
☐ Inotropes present at bedside
☐ Colloid (albumin) at bedside
☐ Ultrasound at bedside Check right internal jugular size, collapse with respiration for volume status, absence of thrombus Check inferior vena cava for collapse
☐ Transesophageal echocardiography: need bicaval view for correct insertion

Laboratory Values

A full coagulation panel should be obtained, including type and crossmatch for 2 to 4 units (depending on the size of the patient, starting hemoglobin levels, and other comorbidities). If hemoglobin is low, blood should be present at the bedside, as significant blood loss can occur during insertion of cannulas.

Medications

Fluids, including colloids and/or crystalloid infusion bags, should be available at the bedside. Syringes with epinephrine 10 µg/mL and 100 µg/mL, as well as a vasopressor for bolus (vasopressin or phenylephrine), should be available for rescue.

VA ECMO patients often receive high doses of inovasopressor infusions for hemodynamic support, leading to endogenous catecholamine depletion as well as up-regulation of adrenergic receptors. Abrupt cessation of these inotropes may cause severe hypoglycemia and other metabolic derangements. We recommend keeping the epinephrine drip at 0.01 to 0.02 µg/kg/min and titrating slowly down.

Heparin is required for anticoagulation of the patient and needs to be given just prior to insertion of the ECMO cannulas. The initial dose is usually 100 U/kg.

Monitoring

Monitoring requires arterial and central lines as well as ultrasound evaluation.

Most patients will already have arterial and central lines present. These lines are essential to ensure immediate hemodynamic feedback as significant amounts of

blood can be lost during cannula insertion. In addition, the central access is necessary to provide inovasopressor administration as indicated.

Ultrasound must be available so clinicians can visualize the veins about to be cannulated and gauge the size of the cannula to be used; the cannula must be big enough to receive at least the smallest sized catheter. In addition, one can survey venous access site to see whether there is vascular collapse of the vein, suggesting a hypovolemic state, or whether a prohibitive thrombus exists within the internal jugular vein, indicating that another site is required.

Echocardiography

Echocardiography can provide valuable information prior to the initiation of ECMO, but the ECMO should not be delayed for unstable patients. For example, a candidate for primarily VV ECMO who exhibits echocardiographic signs of heart dysfunction may benefit from VA ECMO instead.

Echocardiography is also used during placement of the guidewires in the SVC and IVC as well as to adjust the depth and the orientation of the cannulas.

After the initiation of treatment, echocardiography continues to provide valuable information. For VV ECMO, echocardiography can be used to diagnose recirculation of the blood and assess the intravascular volume status (IVC collapse around the cannula). For VA ECMO, echocardiography can give information about the degree of LV recovery, the presence of thrombus around the cannulas or in the cardiac chambers, and the level of LV emptying.

After cannulation, the patient and ECMO circuit are connected. Next, the blood flow is increased until the arterial oxygen saturation is at least 80% for VV ECMO and 90% for VA ECMO. A sample from the venous line during VA ECMO should be targeted to 70%.

MANAGEMENT AND MAINTENANCE

During ECMO management, communication between the different providers plays a paramount role. A very detailed and formal handoff is extremely important, including history of the patient, coagulation and neurological status, and hemodynamic and metabolic goals (Activated clotting time [ACT], mean arterial pressure, near infrared spectroscopy [NIRS], $Pa{O_2}$, $Pa{CO_2}$, pH, HCO_3, hemoglobin and platelet count). The blood type and crossmatch should be kept

current according to hospital protocol (most often every 3 days). The provider should complete an assessment of the patient as well as of the ECMO circuit.

Anticoagulation

Anticoagulation is achieved with an unfractionated heparin drip (goal heparin level: 0.5-0.7 IU/mL). For patients with active bleeding, acceptable heparin levels could be 0.35 to 0.5 IU/mL or an even lower range.

The ACT is measured at the same time as the heparin level and is kept ±20 sec of the ACT during the time of the desired heparin level (usually 180-220 sec).

Heparin when combined with antithrombin III (ATIII) inactivates thrombin (factor IIa) and factor Xa. It also mildly inhibits platelet aggregation.

The activation of platelets from contact with the circuit or from sepsis may contribute to thrombocytopenia, and this must be differentiated from heparin-induced thrombocytopenia (HIT). In patients with HIT, ECMO has been successfully performed by using a direct thrombin inhibitor (bivalirudin or argatroban). Additionally, if the circuit is heparin coated, a circuit exchange should be considered if the immune reaction does not cease.

The goal of the ATIII activity level is 70% to 80%. Correction can be achieved by using the following equation:

Replacement Dose (Units) = (80 – ATIII level) × 0.8 × kg.

Or, a drip can be started at the following dose:

$$(100 - \text{ATIII level})/4 \text{ U/kg/h}.$$

Often, if ATIII activity level is less than 75%, a starting dose of approximately 1,000 U is given.

Laboratory Evaluation

Laboratory values should be determined routinely per unit protocol, and they include arterial blood gas, complete blood cell count, electrolytes, international normalized ratio, heparin and ATIII levels, ACT, and mixed venous saturation (SvO_2).

The goals for vital signs should be set by the team and should include mean

arterial pressure, central venous pressure, and NIRS.

ECMO Circuit Evaluation

The pressure gradient through the oxygenator should be assessed, because an increase of the pressure gradient is an indicator of clot presence and oxygenator failure. A general rule is that a 2-fold increase in the pressure gradient from baseline suggests a problem.

Drug Administration

Drug dosing for a patient receiving ECMO has to be modified due to altered pharmacokinetics. The increased volume of distribution and absorption of the medications by the circuit tubing and oxygenator are responsible for the increased required doses.

Multiple drugs have been studied in terms of use during ECMO, including vasoactive substances, sedatives, analgesics, antiepileptic agents, and antibiotics. The dosing of drugs can be even more complicated in the presence of liver and kidney dysfunction or the presence of ultrafiltration in line with the circuit. The research models were primed with either saline or blood. Lipophilic drugs (fentanyl) were absorbed more than hydrophilic drugs (morphine) and exhibited more variability in absorption between circuits (centrifugal pump circuits with hollow-fiber membrane oxygenator vs roller pump circuits with silicone membranes).

WEANING

Venovenous ECMO

Weaning is attempted once the chest roentgenogram, pulmonary compliance, and arterial saturation have improved suggesting that overall gas exchange is better. Decreasing the fraction of delivered oxygen on the ECMO machine tests the ability of the lungs to oxygenate on their own. Likewise, decreasing the sweep flow tests the ability of the lungs to ventilate and eliminate carbon dioxide. Reducing all sweep gas through the oxygenator to zero eliminates the ECMO support. If the patient tolerates this reduction for a few hours, the decision to decannulate is made. Before decannulation, ventilator settings are adjusted to maintain adequate oxygenation and ventilation after ECMO is discontinued.

An alternative way to wean VV ECMO is by using a bridge tubing from the reinfusion line to the drainage ECMO limb and clamping both cannulas to the patient (**Figures 13** and **14**). The patient is not receiving ECMO support but is still connected to the circuit. Both methods allow the pump to keep circulating blood in a way to avoid clot formation in the circuit or oxygenator.

Figure 13. Primed circuit at the bedside of a pediatric patient

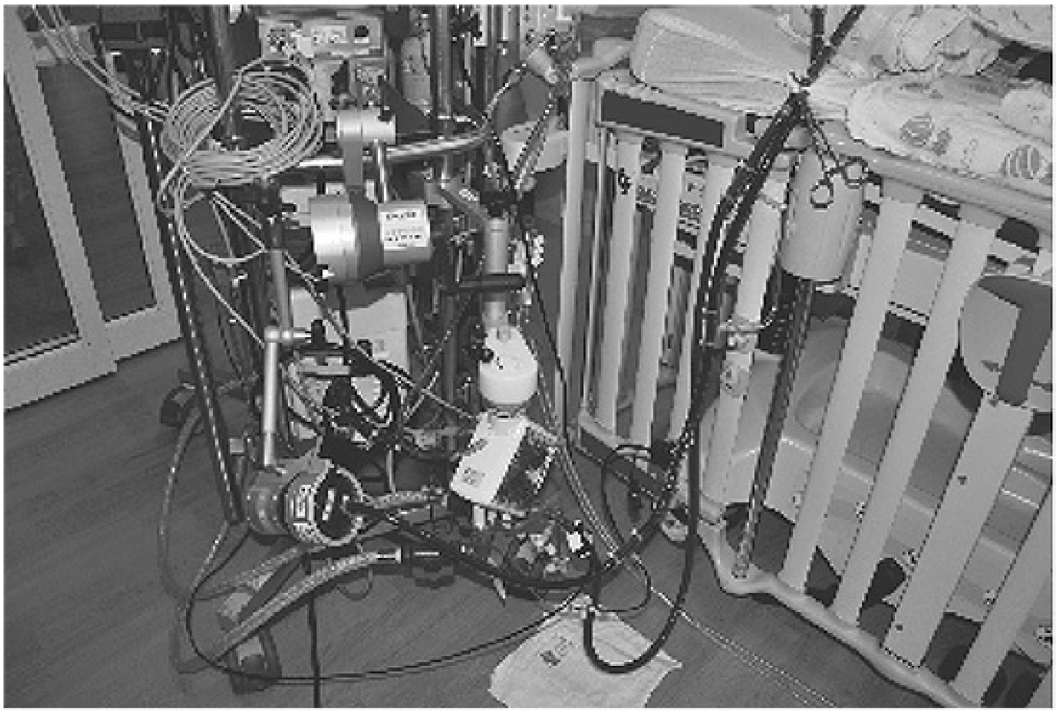

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

Figure 14. The bridge that connects the drainage and the reinfusion tubing

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

Special attention has to be paid to the right ventricular function as the pulmonic vascular resistance may increase rapidly leading to right ventricular failure when the supply of oxygenated normocarbic blood reaching the pulmonic vasculature has decreased.

Venoarterial ECMO

Weaning the patient from VA ECMO is a more complicated process. The patient must exhibit signs of myocardial recovery with consistent opening of the aortic valve. Aortic pulsatility on the arterial line corresponds to improved cardiac output. Inotropic support should be titrated. The flow is reduced to 1 to 1.5 L/min. Clamps are placed on both the drainage and infusion lines while allowing the ECMO circuit to circulate through a bridge between the arterial and venous lines (**Figure 14**). Full anticoagulation with a bolus of heparin may be used prior to the weaning trial to prevent clot formation in the circuit or oxygenator. The goal ACT for the trial and the time that the patient has to maintain hemodynamic stability depend on the center and the individual patient.

TEE during weaning gives valuable information about LV function but can be especially helpful in diagnosing early signs of right ventricular failure, which

can be masked even with the low flows of a weaning trial.

TEE can be used to predict successful weaning during the low-flow trial with an aortic valve volume time integral greater than 10 cm, which estimates the ability of the heart to push the blood forward. Tissue Doppler imaging (TDI) can also assess strength of the heart during systole with lateral mitral annulus systolic velocities (S') greater than 6 cm/s predicting a successful weaning.

TROUBLESHOOTING

The main complications of ECMO are derived primarily from the circuit or from the patient.

Complications Associated With the Circuit

Recirculation of Oxygenated Blood

Recirculation of oxygenated blood can occur during VV ECMO. The first sign is desaturation, and eventually hypercapnia occurs. The close proximity of the tips of the 2 cannulas for double-site cannulation or small rotation of the double-lumen cannula can misdirect the blood and cause recirculation via the drainage cannula. To determine whether recirculation is greatly contributing to the failure to oxygenate, the clinician should check the venous drainage cannula saturation to see whether it is greater than the arterial oxygenation. Slight adjustment of the drainage and return cannulas or rotation of the double-lumen cannula may be sufficient to achieve improvement, and this can be verified by echocardiography.

Cannulation Issues

Problems regarding cannulation can mostly be prevented by inspecting the cannulation sites with ultrasound as previously described.

Circuit Problems

Thrombus formation is the most common complication seen. It can lead to embolization within the patient or oxygenator failure.

a. Air embolism: Multiple sites are available for pressure monitoring, and air-detecting sensors are present as well. Air also can be entrained if the venous cannula is dislodged or the oxygenator membrane is torn. If a large embolus occurs, the sensors attached to the circuit will alarm while shutting down

the pump. Meanwhile, the patient has to be supported via the ventilator and hemodynamically with medications until a new circuit is primed and exchanged.

b. Oxygenator failure: The most common cause of oxygenator failure is progressive deposition of fibrin/thrombus, leading to an increased resistance to flow across the membrane. This is manifested by a transoxygenator pressure gradient. Failure surveillance includes checking pre- and postoxygenator pressures and blood gases (**Figure 15**).

Figure 15. The monitor shows the pre (inlet) and post (outlet) oxygenator pressures

Increase of the gradient between the 2 pressures is an indication of oxygenator failure.

Image courtesy of Kim Chapman, Visual Information Specialist, Clement J. Zablocki VA Medical Center.

c. Hemolysis or disseminated intravascular coagulation: This can be caused by fibrin deposits on the oxygenator membrane, high turbulent pump flow, excessive heat generation in the pump head, high negative suction on cannulas due to hypovolemia, or circuit thrombosis. Elevation in free hemoglobin, LDH, and decrease in the haptoglobin suggests this diagnosis.

Circuit Heater

Problems with the circuit heater can include low water levels or cracked tubing.

Bleeding

Tubes and connectors can rupture or become damaged, although this is less common with newer, improved tubing. Stopcocks can be left opened accidentally. If bleeding is severe, hypotension in a previously stable patient is noted.

Loss of Circuit Flow

This is usually caused by hypovolemia or venous cannula malposition. An increase in the negative inlet pressure indicates a drainage problem. The first step is to decrease the circuit flow to disengage the suction being applied from the vessel on the cannula, followed by a volume challenge. Inadvertently placed clamps that were recently added or kinking of the cannulas can lead to decreased venous flow. Of course, patient issues such as pneumothorax, hemothorax, or pericardial tamponade should be quickly ruled out with a chest radiograph or echocardiogram.

Left Ventricular Distension

Pulsatility is an extremely important factor for VA ECMO management. If the pump output is high or the systemic vascular resistance is increased, the LV cannot overcome the pressure in the aorta. The aortic valve does not open, and pulsatility is lost. This causes distention of the LV, increased wall tension, and higher oxygen consumption with lower coronary perfusion pressure. This process can also increase the risk of thrombus formation in the cardiac chambers and especially in the LV. Emptying of the LV is very important and, most of the time, is verified by pulsatility. When the reinfusion cannula is placed centrally through a sternotomy, an LV vent can be placed through the pulmonary vein to decompress the LV. This is especially important for patients with ischemic acute heart failure or ischemic cardiac arrest, because it minimizes oxygen consumption and improves the coronary perfusion pressure, allowing recovery of myocardial function. With myocardial recovery comes increased wall motion. The first step in weaning is to decrease or stop the drainage of the LV vent and resume a small degree of pulsatility. In pediatric patients with carotid or internal jugular cannulation, the LV can be decompressed by a balloon atrial septostomy.

Complications Associated With the Patient

1. Bleeding (gastrointestinal tract, surgical site, cannulation site, intracranial)
2. Hemodynamic instability (**Tables 2 and 3**)
3. Infection

Table 2. Causes of Hypoxia During ECMO

Oxygenator failure: exchange oxygenator or if transmembrane pressure >50 mm Hg.
Low fraction of delivered oxygen or sweep flows on the blender, empty cylinder
Recirculation for VV ECMO: reposition cannulas, adjust pump flow
Low ECMO flows a. Hypovolemia resulting in less oxygenated blood b. Sepsis c. Decreased revolution per minute d. Cannula kink, small cannula size, thrombus e. High (for VA ECMO): sedation or afterload reduction
Anemia: keep hemoglobin closer to 10 mg/dL if persistently low oxygen saturation
Worsening of lung function, pneumothorax, pneumonia, pleural effusion
Increased oxygen demand

Table 3. Causes of Hypotension During ECMO

Sepsis
Hypovolemia (consider fluid bolus or transfusion; assess for internal bleeding: gastrointestinal tract, abdomen, thorax, brain)
Increased afterload (consider afterload reduction or sedation)
VV ECMO (consider failure of the right or left side of the heart, tamponade, myocardial ischemia)
VA ECMO oxygenator failure would increase the resistance and reduce the flow

Every ECMO patient is at risk for ECMO failure, and the team should always be prepared to wean from ECMO until the technical issue is solved. During this unfortunate situation, inotropes and blood products must be available and the

providers must be prepared to wean or switch circuit.

SUMMARY

Early recognition of the indications for ECMO and appropriate selection of candidates have improved the outcomes of both refractory cardiogenic shock and severe cases of ARDS. It remains to be established which ARDS patients are best suited for ECMO, and earlier use (<7 days) may have the best outcomes. Advanced biomedical engineering, the improved safety profile of the equipment, and the increased level of ICU care will make ECMO even more effective.

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CHAPTER 17

Airway Management

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Key words: airway, noninvasive ventilation, endotracheal intubation

Airway management is aimed at providing ventilation and oxygenation. In the ICU, the ability to accurately predict the need for airway intervention and to select the optimal strategy for a particular patient is essential. This chapter focuses on material relevant for board examination while exploring each topic in the context of practical clinical application. Proficiency in airway management can be conceptualized as a combination of knowledge and manual skill. Although there is little substitute for deliberate practice and specialty training in airway management, a systematic understanding of airway techniques serves as the basis on which safe airway management skills are built.

AIRWAY EVALUATION

In the acute care setting, the urgent need for airway management may necessitate expeditious airway evaluation. The ability to efficiently and summarily perform an airway evaluation is based on an understanding of assessment principles that have been routinely rehearsed in nonurgent circumstances.

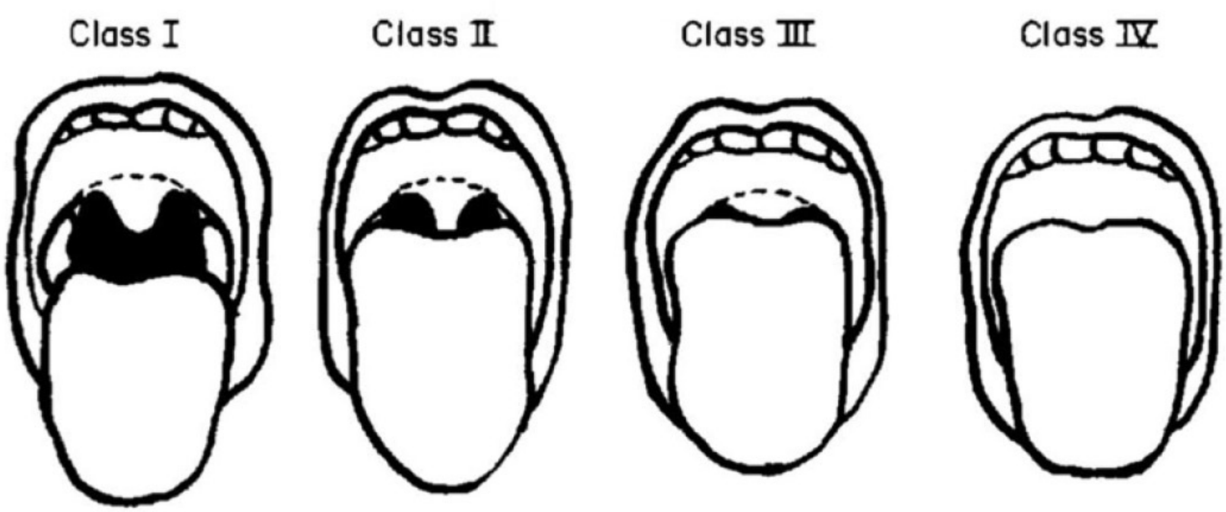
History

A history of difficult airway should always raise concern for difficulty with future airway management. Even if prior airway management was straightforward, the possibility of future difficult airway management cannot be dismissed. The ease of mask ventilation and the use of airway instruments and medications should be noted.

Routine Evaluation and Prediction of Difficulty With Airway Management

Routine airway evaluation typically includes the Mallampati/Samsoon-Young classification (**Figure 1** and **Table 1**), cervical spine mobility, temporal mandibular joint function, state of dentition, and pathological features of the nose, mouth, and neck. Independent predictors of difficult mask ventilation are age older than 55 years, body mass index greater than 26 kg/m^2, lack of teeth, presence of beard, and history of snoring. Impossible mask ventilation may be predicted by the presence of neck radiation changes, male gender, diagnosis of sleep apnea, Mallampati/Samsoon-Young classification III or IV, and presence of a beard. Concern for difficult intubation (DI) should be raised with any of the following findings on examination: increased length of upper incisors, mandible anterior to maxillary incisors, mouth opening less than 3 cm, inability to visualize uvula when the patient's tongue is protruded, arched or narrow palate, mandibular space fullness, thyromental distance shorter than 3 finger breadths, short sternomental distance (<12 cm), thick neck (>40 cm), diminished cervical spine flexion and/or extension, and limited mandibular protrusion. While no prediction model is perfect, as the number of predictors of DI increases so does the probability of DI. DI may be predicted by increasing Mallampati/Samsoon-Young classification combined with diminished thyromental distance.

Figure 1. Mallampati/Samsoon-Young classification



From Samsoon GLT, Young JRB. *Anaesthesia.* 1987;42:487-490. Used with permission.

Table 1. Mallampati/Samsoon-Young Classification

Class	Structures Visualized

I	Uvula, fauces, pillars, soft palate
II	Uvular, fauces, soft palate
III	Soft and hard palate
IV	Hard palate only

The MACOCHA score has been validated for predicting difficulty with intubation via direct laryngoscopy specifically in the ICU. The MACOCHA score is comprised of the following elements: Mallampati score III or IV (5 points), obstructive sleep apnea syndrome (2 points), and 1 point each for reduced mobility of cervical spine, mouth opening less than 3 cm, comatose patient, oxygen saturation less than 80%, and nonanesthesiologist operator. Higher score predicts difficulty, with DI occurring in 36% of patients with a score 3 or higher and in 2% of patients with a score less than 3.

NONINVASIVE AIRWAY MANAGEMENT

A range of ventilation and oxygenation problems in the critical care environment can be addressed by noninvasive means. At times these techniques may be the treatment plan in and of themselves, and at other times noninvasive management serves as a temporizing measure until a definitive airway can be established.

Oxygen Supplementation

Standard nasal cannula provides 100% oxygen at flow rates typically less than 6 L/min. The approximate FIO_2 (fraction of inspired oxygen) with nasal cannula is 0.21 plus 0.04 for each L/min.

High-flow nasal cannula provides humidified oxygen at flows up to 60 L/min, FIO_2 up to 1.0, and varying levels of continuous positive airway pressure (CPAP). The role of high-flow nasal cannula in respiratory failure is unclear as the evidence of efficacy is mixed.

Face masks come in numerous varieties. A simple face mask fits loosely on the face, runs on 100% oxygen at flow rates of 5 to 10 L/min, and has a ceiling FIO_2 of 0.60. Well-fitting masks with reservoir bags allow the patient to breath only the gas in the bag provided the flow rate is adequate (partial rebreathing mask, FIO_2 maximum ~ 0.8) or provided the device contains several 1-way valves

(nonrebreathing mask, FIO_2 maximum 1.0).

Manual Face Mask Ventilation

For the patient with poor ventilation, noninvasive oxygenation alone will be inadequate. A manual resuscitation bag-valve device, when properly applied to the face for mask ventilation, can overcome obstruction and provide oxygenation and ventilation in some circumstances. This is frequently done in an effort to support a patient during life-threatening airway or respiratory dysfunction while preparations are made for more advanced airway management. However, evidence demonstrates that critically ill patients in whom noninvasive respiratory support fails will have little improvement in blood oxygen tension with manual mask ventilation. Manual face mask techniques may noninvasively support a patient's oxygenation and ventilation temporarily during conditions that are brief or rapidly reversible (eg, oversedation).

Noninvasive Positive Pressure Ventilation

The delivery of supplemental oxygen alone does not address excessive work of breathing, hypercarbia, and hypoventilation. Under some conditions, these problems can be managed by noninvasive positive pressure ventilation (NIPPV) administered mechanically via face mask, nasal mask, or helmet. NIPPV provides oxygenation and ventilatory support by CPAP, pressure support ventilation, volume-cycled ventilation, or pressure-cycled ventilation. Indications include acute respiratory distress and acute hypercapnia. NIPPV is superior to mask ventilation at reducing desaturation when used for preoxygenation prior to intubation of critically ill patients with acute hypoxic respiratory failure. In principle, patients with a condition that can be reversed in less than 48 hours can benefit the most from continuous NIPPV. Facial structure that is conducive to a mask (if a helmet is not being used) and a level of consciousness that supports at least some patient cooperation are additional practical factors to consider. Specific contraindications to NIPPV include cardiac or respiratory arrest, particular nonrespiratory organ failure (severe encephalopathy, severe upper gastrointestinal bleeding, hemodynamic instability), facial surgery, upper airway obstruction not relieved by positive pressure, inability to cooperate or protect airway, inability to clear airway secretions, and high risk of aspiration. Upper airway obstruction related to obstructive sleep apnea is generally not considered a contraindication to NIPPV.

Evidence for NIPPV Use in COPD

The benefits of NIPPV have been shown most conclusively in patients with acute respiratory failure related to exacerbation of chronic obstructive pulmonary disease (COPD). It has been found that NIPPV reduces the risk of intubation and in-hospital mortality among patients with exacerbation of COPD, especially those with respiratory acidemia. In a Cochrane review comparing weaning of predominantly COPD patients by invasive positive pressure ventilation versus early extubation with immediate application of NIPPV, the NIPPV strategy showed reductions in mortality, ventilator-associated pneumonia, length of stay in ICU and hospital, total duration of ventilation, and duration of endotracheal mechanical ventilation.

Evidence for NIPPV Use in Non-COPD Acute Respiratory Failure

A systematic review of randomized controlled trials sampling a diverse patient population with acute hypoxemic respiratory failure found that when NIPPV was added to standard care, reductions in the rate of endotracheal intubation, ICU length of stay, and ICU mortality were observed. The authors cautioned that some subgroups of patients will benefit whereas others may be harmed by NIPPV. As such, the routine use of NIPPV in all patients with acute respiratory failure is not supported. Patients with acute cardiogenic pulmonary edema who are treated with NIPPV have a reduced need for intubation and more rapid improvement compared with patients receiving standard oxygen therapy. Some data suggest that NIPPV can be used selectively to help wean a patient from mechanical ventilation, avoid reintubation, support acute exacerbations of obesity-hypoventilation syndrome, and manage the patient with a “do not intubate” care directive who has a potentially reversible cause of respiratory failure.

Complications of NIPPV

Patient discomfort, anxiety, development of facial skin lesions, and aerophagia are common complications of NIPPV. Delivery of NIPPV by helmet is associated with greater patient tolerance and fewer complications than delivery by face mask. Application of airtight foam and/or adhesive skin dressings can improve comfort and retard the development of skin lesions with face mask NIPPV. Aerophagia is typically benign. Placement of a nasogastric tube is not required during NIPPV and can disrupt the seal of the device.

INVASIVE AIRWAY MANAGEMENT

Indications for Endotracheal Intubation

Endotracheal intubation (ETI) in the ICU usually is necessitated by airway obstruction not relieved by simple maneuvers, inability to clear the airway of secretions, loss of protective airway reflexes, and respiratory failure. In keeping with these indications, establishing an endotracheal airway serves as a means to provide ventilation and oxygenation, protect the airway from fluids, create a conduit for access to the bronchial region for suctioning, and visualize the airway through bronchoscopy.

Preparation for Endotracheal Intubation

Creation of a Plan and Mobilization of Resources

The plan, personnel, and equipment must be tailored to provide the maximum chance of safe, successful ETI on the first attempt in critically ill patients. The literature shows that making more than 2 laryngoscopic attempts is associated with a significant increase in complications in critically ill patients. When time allows, the clinician should review the patient's prior airway management and perform a focused airway examination. Regardless of urgency, it is essential to develop a primary plan, contingencies for difficulty, and a backup plan for invasive airway management. The plan should take into account the likelihood of difficult mask ventilation and the likelihood of difficulty with ETI. Furthermore, the skill and experience of the bedside provider and the availability of providers specifically trained in airway management must be considered in the context of urgency. In nonemergent conditions, the need for trainees or other inexperienced providers to learn airway management should be considered, although enthusiasm for teaching and learning must be tempered against risk to the patient. Mustering specialized assistance earlier rather than later can dramatically affect patient outcome. Similarly, collecting necessary airway equipment and medications can take time in the ICU. All ICU providers should know where the airway supplies are stored and what the local policy is for expediting the retrieval of essential airway supplies. Under some nonemergent circumstances, it may be appropriate to consider transporting the patient to an operating room so that a broad selection of airway equipment can be immediately available and a surgical team can be on standby for surgical airway intervention.

Protocolized airway management in the ICU has been linked with reduced complications. Following an algorithm helps to ensure that a specific plan with contingencies is in place and is understood by all involved in the airway management. Published protocols include items such as use of MACOCHA score to predict difficulty, the presence of 2 operators, the role of videolaryngoscopy and supraglottic airways, rapid sequence induction, and mandatory steps for preventing and managing hypotension. Please see the Suggested Reading list for more on this topic.

Selection of Medications for ETI in the ICU

Critically ill patients frequently have a limited physiological reserve, making them susceptible to hemodynamic instability and hypoxemia with the administration of medications for airway management. A working knowledge of drugs commonly used for airway management allows the provider to select the pharmacological intervention that is optimal for a specific patient. Intubation without pharmacological intervention or with only airway topical anesthesia can be considered for obtunded and comatose patients. For ease of comparison and study, **Table 2** summarizes the most frequently used medications.

Table 2. Properties of Medications Frequently Used for Airway Management in the ICU

Drug	Class	Primary Mechanism of Action	Cardiovascular Effects	Respiratory Rate	ICP	Notes
Propofol	Hypnotic	GABA potentiation	Myocardial depression ↓↓↓ MAP	↓↓↓	↓↓↓	• Ra ar • He re ha or
Etomidate	Hypnotic	GABA potentiation	0/↓ MAP	0/↓	↓↓↓	• Ra ar • Ca su us in
Ketamine	Dissociative	NMDA antagonist	↑↑ HR	0/↓	↑↑↑	

			↑↑ MAP			• Pr ar se • Si gl to se
Dexmedetomidine	Hypnotic	α_2 agonist	↓↓–↓↓↓ HR ↓ MAP	0/↓	*	• Pr ar se
Midazolam	Benzodiazepine	GABA potentiation	0/↑ HR ↓ MAP	↓–↓↓	↓↓	• Du ef in he ar ag
Fentanyl	Opioid	Opioid receptor agonist	↓ HR 0/↓ MAP	↓↓–↓↓↓	0/↑	• Hi of in ca dy
Succinylcholine	Depolarizing NMB	AChR agonist	↓ HR	↓↓↓	0/↑	• Ve ar ac fo • Co in rh hy or cr h
Rocuronium	Nondepolarizing NMB	AChR competitive antagonism	0/↑ HR 0/↓ MAP	↓↓↓	0	• Ra • Su wi

						dc
Sugammadex	NMB reversal	Chelation of steroidal NMB	0	↑↑↑	0	• Ul re st (e ro • N in pc • A us 20

Abbreviations: AChR acetylcholine receptor; GABA, *y*-aminobutyric acid receptor; ICP, intracranial pressure; HR, heart rate; MAP, mean arterial pressure; NMB neuromuscular blocker; NMDA, *N*-methyl-D-aspartate receptor; RSI, rapid sequence induction; SCI, spinal cord injury. 0 no effect; ↑ increase; ↓ decrease; * sparse evidence.

Endotracheal Tube Selection

Endotracheal (ET) tubes are sized by internal diameter and length. Size of the ET tube is normally 8.0 mm for a typical adult and 7.0 mm for a small adult, with smaller sizes sometimes being necessary for nasotracheal intubation. Because the glottis is the narrowest part of the adult upper airway, passage of an ET tube through the glottis requires thoughtful consideration of tube caliber and demands close attention to the mechanics of placing the ET tube to minimize tissue trauma. Routine practice is to place the largest diameter ET tube that avoids circumferential contact with the structures surrounding the glottis.

The functions of the ET tube cuff are to create a seal for positive pressure ventilation, center the ET tube in the airway by uniform inflation, and prevent aspiration. The standard cuff used for a critically ill adult is a high-volume–low-pressure design. Cuff pressures of 20 to 30 cm H_2O ideally prevent microaspiration while minimizing cuff-related complications such as tissue necrosis, erosion, and tracheal rupture. Tissue necrosis theoretically occurs when cuff pressure exceeds capillary pressure (approximately 32 mm Hg). A number of devices are available to measure or limit cuff pressure, which should be checked after intubation and periodically thereafter. Tapered design of the cuff may reduce microaspiration, and antiseptic-impregnated ET tubes may reduce the bacterial colonization of the airway. Finally, ET tubes with a suction device

to remove subglottic secretions may reduce ventilator-associated pneumonia.

Essential Airway Equipment

An airway cart stored in the ICU can dramatically decrease the time required to collect equipment for intubation. Even for the most parsimonious provider, the equipment necessary to execute the primary and backup airway management plans should be gathered. Basic equipment includes oxygen supply, face mask, bag-valve device with a positive end-expiratory pressure valve, suction apparatus, ET tubes of various sizes, ET tube stylet, oral airways, nasal airways, laryngoscopes or videoscopes of various sizes, syringe for cuff inflation, and tape. An end-tidal carbon dioxide detector, Magill forceps, local anesthetics, airway topicalization devices, and tongue depressors are all very useful adjuncts that can be difficult to locate when suddenly needed. The patient's room should be checked for the required equipment as well as adequate lighting and space to accommodate personnel and equipment.

Endotracheal Intubation Techniques

Preoxygenation

In elective situations, ETI is typically preceded by preoxygenation (denitrogenation), the practice of having the spontaneously breathing patient inhale 100% oxygen by sealed face mask for several minutes prior to induction. The inhaled oxygen replaces the nitrogen in the patient's functional residual capacity, thereby creating a reservoir of oxygen that prolongs the onset of hypoxemia during apnea. In critically ill hypoxemic patients, manual face mask oxygenation is inferior to NIPPV for preventing desaturation during intubation attempts. Truly emergent conditions may call for immediate progression to intubation without preoxygenation.

Selecting Orotracheal or Nasotracheal Intubation

Orotracheal intubation is more commonly performed in the ICU than is nasotracheal intubation. Nasotracheal intubation is contraindicated in patients with significant coagulopathy, cerebrospinal rhinorrhea, basilar skull fractures, anatomic abnormalities that can obstruct passage of the tube, and paranasal sinus infection. Bleeding from nasal placement of the tube is common and generally self-limited. Necrosis of the tip of the nose is an ongoing risk as well. The oral route compromises the routine care of the oral cavity and pharynx. In general,

the oral route appears to be less fraught with complications and is the preferred route for the patient expected to have prolonged intubation (multiple days).

Intubation by Direct Laryngoscopy

Direct laryngoscopy (DL) is frequently used for orotracheal intubation. Nasotracheal intubation can also use DL once the tip of the ET tube is visualized in the airway. Following the previously described preparations for ETI, the operator positions the patient's head in "sniffing position" for optimal DL. Sniffing position involves flexion of the neck and slight extension at the atlanto-occipital joint, theoretically resulting in alignment of the oral, pharyngeal, and laryngeal axes; however, the value of this position has been questioned. With the patient's head positioned, the operator uses a laryngoscope handle and blade to view the glottis. The ET tube is advanced through the aperture in the vocal cords and the cuff is inflated.

The ease of ETI by DL can be augmented by several mechanisms:

- A stylet in the lumen of the ET tube allows the operator to form the desired curvature and increases the rigidity of the ET tube.
- An ET tube guide or long stylet can be used to gain access to the glottis when DL does not afford a favorable view, with the ET tube being advanced over the guide and through the glottis.
- The BURP maneuver (backward-upward-rightward pressure) applied exteriorly to the larynx improves the view of the laryngeal aperture.

Alternatives to Direct Laryngoscopy

An increasing number of techniques and devices are available for airway access. Most of these overcome the limitations of DL. An exhaustive listing is available free of charge through online access to *Anesthesiology News* (www.anesthesiologynews.com). Common alternatives to DL include the following:

- *Video laryngoscopes* function in a similar fashion to standard laryngoscopes with a fiberoptic view produced on a video screen. Even for an experienced laryngoscopist, the use of video laryngoscopy may require practice to gain proficiency. Use of videolaryngoscopy appears to reduce airway management complications in the ICU when compared with DL.

- *Supraglottic airway devices* such as the laryngeal mask airway (LMA Company, Henley, UK) are available in many varieties. They are rarely used to maintain an airway for an extended period of time. Their use in the ICU is principally for ventilation when mask ventilation fails and as a conduit for ETI.

- *Fiberoptic airway devices* can be used for laryngoscopy. Direct rigid fiberoptic laryngoscopes (video laryngoscopes) and flexible fiberoptic bronchoscopes can be used to achieve ETI under a great variety of adverse airway conditions.

- *Retrograde intubation* involves inserting a needle or angiocatheter through the cricothyroid membrane or lower, passing a wire or epidural catheter cephalad until it protrudes from the mouth, and advancing an ET tube over this conduit.

- *Cricothyrotomy* and *tracheostomy* are used to gain access to the airway through percutaneous Seldinger technique or by incision.

Rapid Sequence Induction

Rapid sequence induction (RSI) is a technique to minimize the time elapsed between loss of consciousness and ETI. The premier purpose is to limit the risk of aspiration of gastric contents. Standard practice in RSI is to preoxygenate, provide induction medications for rapid onset with or without a neuromuscular blocking agent, avoid positive pressure mask ventilation, and intubate with a cuffed ET tube. In concept, the application of cricoid pressure occludes the esophagus, thereby minimizing the risk of aspiration of stomach contents, although it may also obscure the view of laryngoscopy. Evidence for its use is mixed.

Confirmation of Endotracheal Intubation

No perfect test is available to determine the placement of an ET tube. The classic confirmations of ETI are symmetrical chest movement with positive pressure ventilation, condensation in the ET tube, sustained detection of end-tidal carbon dioxide, and auscultation of bilateral breath sounds. None of these indicators are considered failsafe. Colorimetric end-tidal carbon dioxide detection is considered almost failsafe. Direct vision of the ET tube between the vocal cords and flexible fiberoptic bronchoscopy through the ET tube visualizing tracheal rings and carina are considered reliable indicators of ETI. Evidence suggests that

auscultation is less sensitive at detecting endobronchial intubation than is simple observation of ET tube depth. An ET tube depth of 20 to 21 cm for women and 22 to 23 cm for men is recommended. Additionally, advancing the ET tube under laryngoscopy such that the cuff is 2 cm deeper than the vocal cords reliably places the ET tube tip in the middle of the trachea. Emerging evidence suggests that cuff inflation detected by ultrasound Doppler signal at the suprasternal notch correlates with a properly placed ET tube. Chest radiography and fiberoptic bronchoscopy through the ET tube can also assist with proper positioning.

Complications During Endotracheal Intubation

Intubation can precipitate tachyarrhythmias, bradyarrhythmias, hypotension, and hypertension. By knowing the pathophysiological status of the patient, the clinician can prevent or reduce these effects by careful pharmacological selection. Other complications include trauma to any of the airway structures, distal dislodgement of a foreign body, trauma to the eyes or cervical spine, and esophageal or endobronchial intubation.

AIRWAY MANAGEMENT IN THE INTUBATED PATIENT

Exchange of Endotracheal Tubes

Circumstances necessitating the exchange of one ET tube for another include the need for a larger lumen ET tube (eg, to accommodate bronchoscopy), occlusion of the lumen of an ET tube, cuff rupture, and need for a different type of ET tube. As with intubation, the provider should have at least 2 plans, mobilize resources, and select the appropriate pharmacological intervention based on the patient and the anticipated response to airway manipulation. One technique for exchanging ET tubes is to simply remove the existing ET tube and reintubate with the desired ET tube. Another method is to load a fiberoptic bronchoscope with an ET tube, advance this bronchoscope through the vocal cords while the extant ET tube remains in place, remove the old ET tube, and advance the new ET tube over the bronchoscope. Finally, a number of stylets, airway obturators, and tube exchangers can be used. These are generally semirigid devices that can fit through the lumen of an ET tube and are long enough that the operator can pass the tip distal to the end of the ET tube while having sufficient length outside of the patient for control. These devices may come with a lumen and orifices for jet ventilation or low-pressure oxygen administration.

Extubation

Criteria for extubation can generally be simplified to resolution of the initial indications for intubation to the extent that intubation is no longer necessary, assuming a new indication has not developed. In general, extubation is appropriate when there is (1) absence of airway obstruction, (2) adequate secretion control, (3) presence of protective airway reflexes, and (4) absence of respiratory failure.

Extubation Maneuvers

With extubation, as with intubation, a plan and equipment should be prepared for the possibility of failure. The patient should be alert and informed of the plan for extubation, the head of the bed raised to greater than 45°, the pharynx suctioned, and the ET tube cuff deflated. Positive pressure should be applied as the ET tube is removed.

Extubating a patient who has demonstrated or suspected difficult mask ventilation or DI warrants careful planning. Under some circumstances it may be appropriate to extubate over a stylet or tube exchanger to maintain a conduit to the airway for rapid reintubation. Patient tolerance for this is enhanced by applying topical anesthetic either directly to the airway or onto the device itself.

Complications With Extubation

Postextubation stridor can indicate airway edema or laryngospasm. Airway narrowing related to edema can frequently be predicted before extubation by a “leak test,” in which the ET tube cuff is deflated and the expiratory volume is subtracted from the inspiratory volume measured prior to cuff deflation. Leak volumes less than 110 mL, female gender, relatively small tracheal diameter, large ET tube size, and extended duration of ETI have been identified as risk factors for postextubation stridor and subsequent reintubation. The value of nebulized epinephrine and steroids to prevent or treat postextubation stridor is unclear.

Complications of Prolonged Endotracheal Intubation

Damage to surrounding structures is a clear risk of maintaining an ET tube in the airway. This can manifest as temporary sore throat or hoarseness after extubation, prolonged hoarseness (vocal cord paralysis), loss of tongue sensation (hypoglossal nerve trauma), airway bleeding (erosion into nearby vascular

structures), and gastric contents in the airway (erosion into the esophagus). Tracheal stenosis can present with stridor even months following extubation. Other complications include occlusion of the ET tube by kinking, dried secretions, or the patient biting the ET tube. Ventilator-associated pneumonia appears to be related to the presence of an ET tube and the duration of mechanical ventilation. Additionally, ET tube migration resulting in endobronchial intubation or location of the ET tube tip at or above the vocal cords can occur. Finally, unplanned extubation by providers or patients is possible. For the patient who has been or will remain intubated for a prolonged period, a tracheostomy should be considered, although the optimum timing of this remains controversial.

SPECIAL CONSIDERATIONS IN AIRWAY DECISION MAKING

ICU patients may require considerations outside of routine airway management. A suspicion for nonroutine ETI should be raised by dueling priorities in management, abnormal airway structure, emergent conditions, and laryngeal or tracheal trauma.

Upper Airway Obstruction

Partial or complete obstruction of the upper airway can compromise ventilation. Partial obstruction of the upper airway can be identified by stridor as well as retractions of the soft tissues of the neck and intercostal muscles during inspiration. Total obstruction is marked by the complete absence of gas movement within the airway and failure of the chest to expand despite inspiratory effort. Primary causes of upper airway obstruction include pharyngeal collapse, foreign substances, and laryngospasm. Pharyngeal collapse can result from obstructive sleep apnea, diminished genioglossus muscle tone (sedation, obtundation), or a space-occupying lesion (tumor, edema, abscess, hematoma). Secretions, blood, vomit, or a foreign body contacting the larynx can precipitate laryngospasm, most often identified by inspiratory stridor.

In many cases, upper airway obstruction can be treated immediately. Two maneuvers relieve upper airway obstruction: extension at the atlanto-occipital joint and jaw thrust by forcing the mandible anteriorly via pressure on the mandibular rami. Carefully applied jaw thrust can be performed successfully in patients with cervical injury for whom chin lift is not an option. Failure of these maneuvers should prompt the use of a nasopharyngeal airway (or oropharyngeal airway). A nasopharyngeal airway is a soft, flexible tube with a flange on one

end to prevent overly deep insertion. It stents open the soft tissues of the nasopharynx and oropharynx after being advanced through a nares. An oropharyngeal airway has a shape similar to that of the oral cavity and upper oropharynx, comes in a variety of sizes, and typically has a lumen. It creates a passageway by pushing the tongue and airway soft tissues aside. Both of these airway devices are intended for temporary use and can cause local trauma.

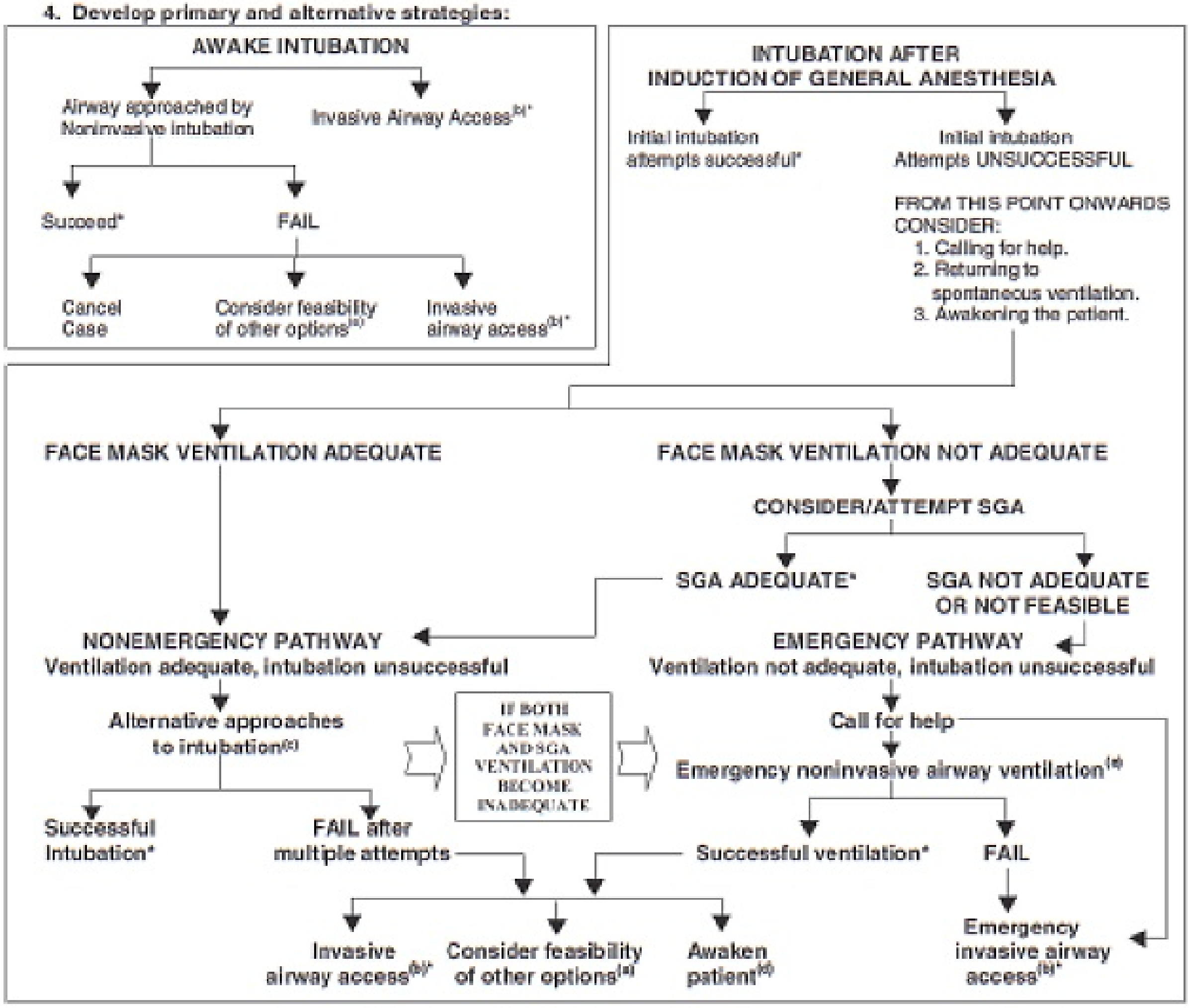
After all maneuvers and airway adjunct devices have been applied, airway obstruction may persist. If foreign body obstruction is the known or suspected cause of total airway obstruction, abdominal thrusts may provide relief in the conscious patient. If laryngospasm is suspected, management entails removing the prompting stimulus (if feasible), applying positive airway pressure until cessation of spasm, deepening the level of anesthesia or sedation, administering muscle relaxants, or performing ETI. Even if premanagement airway evaluation did not generate concern for difficult or impossible ventilation, failure of all of the noninvasive maneuvers and adjunct devices described here to resolve airway obstruction must be rapidly recognized as a “cannot ventilate” situation.

The Difficult Airway

DI has been shown to be associated with complications and severe morbidity in the ICU. Efforts should be focused on both predicting difficulty and making plans to manage difficulty when encountered. The specifics of examination in predicting airway difficulty were detailed earlier. Of particular note, the MACOCHA score for predicting difficulty with intubation contains only one modifiable factor—operator type. For MACOCHA scores of 3 or higher, seeking the assistance of an anesthesiologist is prudent. Similarly, the presence of an expert in surgical airway increases successful management of the difficult airway. The American Society of Anesthesiologists (ASA) Difficult Airway Algorithm from the 2013 ASA practice guidelines (**Figure 2**) demonstrates the critical decision points for airway management. Although these themes are true for all airway management scenarios, protocols specifically designed for airway management in the ICU are available as well (see Suggested Reading list).

Figure 2. Difficult Airway Algorithm (ASA-DAA)

1. Assess the likelihood and clinical impact of basic management problems:
    - Difficulty with patient cooperation or consent
    - Difficult mask ventilation
    - Difficult supraglottic airway placement
    - Difficult laryngoscopy
    - Difficult intubation
    - Difficult surgical airway access
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.
3. Consider the relative merits and feasibility of basic management choices:
    - Awake intubation *vs.* intubation after induction of general anesthesia
    - Non-invasive technique *vs.* invasive techniques for the initial approach to intubation
    - Video-assisted laryngoscopy as an initial approach to intubation
    - Preservation *vs.* ablation of spontaneous ventilation
4. Develop primary and alternative strategies:



*Confirm ventilation, tracheal intubation, or SGA placement with exhaled CO_2.

a. Other options include (but are not limited to): surgery utilizing face mask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous airway, jet ventilation, and retrograde intubation.

c. Alternative difficult intubation approaches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMA or ILMA) as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Emergency non-invasive airway ventilation consists of a SGA.

American Society of Anesthesiologists Difficult Airway Algorithm. (ASA-DAA). Practice Guidelines for Management of the Difficult Airway: An updated report by the American Society of Anesthesiologists Task Force on management of the difficult airway. *Anesthesiology.* 2013;118:251-70. Used with permission.

Full Stomach

The possibility of a full stomach creates a competing priority in the management of the airway. The full stomach increases the risk of aspiration. A multitude of conditions are thought to promote a full stomach: fasting less than 6 hours, altered consciousness, trauma, diabetes (gastroparesis), morbid obesity, pregnancy, and elevated intracranial pressure (ICP). Principles of management include selecting awake intubation or RSI. Awake intubation in a patient with combined full stomach and known or predicted difficult airway is prudent. RSI is a traditional solution, albeit without sound data to support its use.

Obstetric Patient

All obstetric patients are considered to have a full stomach. Additionally, physiological changes of pregnancy can increase the difficulty of mask ventilation and ETI. Airway edema, friable airway tissue, and enlarged breasts can complicate airway management during pregnancy and the postpartum period. A diminished functional residual capacity can shorten the duration of apnea that results in hypoxemia. As a principle of care, the life of the mother has higher priority than delivery of the fetus.

Obesity

Mask ventilation can be difficult in obese patients given the effect of habitus on decreasing airway compliance and a tendency toward upper airway obstruction. Obese patients experience oxygen desaturation more rapidly than do nonobese patients. Preoxygenation in the reverse Trendelenburg position and application of positive end-expiratory pressure have been shown to prolong the duration to desaturation during apnea in obese patients. Finally, ETI can be more difficult in obese patients, predicted primarily by neck circumference greater than 43 cm.

Elevated Intracranial Pressure

High ICP presents a dueling-priority issue in airway management. The objective is to select the proper medications, in the proper sequence, such that neither the

medications nor the intubation stimulus further raises ICP. Methods to accomplish this include avoiding ketamine, using induction medication to blunt sympathetic response to airway stimulus, and continuing blood pressure management if hypertension results from airway stimulation. Although succinylcholine may raise ICP, this has not been consistently demonstrated. If awake intubation is performed in the patient with elevated ICP, adequate topicalization of the airway must be ensured to minimize sympathetic discharge during intubation.

SUMMARY

Critically ill patients tend to have compromised physiological reserve and frequently require emergent airway intervention. This combination creates a high risk of difficulty with airway management in the ICU. Consequently, a firm command of airway knowledge can bolster the clinician's ability to identify the need for airway intervention, predict the likelihood of difficulty, and generate the optimal plan for airway intervention.

SUGGESTED READING

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Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology.* 2013;118:251-270.

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CHAPTER 18

Arterial Blood Gas Interpretation, Capnography, and Pulse Oximetry

Eric Ursprung, MD, and Theofilos P. Matheos, MD

Key words: hemoglobin dissociation curve, alveolar gas equation, P/F ratio, red and infrared wavelengths, methemoglobin and carboxyhemoglobin, capnography, end-tidal carbon dioxide

When you arise in the morning, think of what a precious privilege it is to be alive—to breathe, to think, to enjoy, to love.

Marcus Aurelius (121-180 AD)

ARTERIAL BLOOD GAS INTERPRETATION

Blood gas interpretation is an essential part of critical care practice. Expertise in blood gas interpretation crosses over specialties such as anesthesiology, cardiology, pulmonology, and nephrology, among others (**Table 1**).

Table 1. Definitions of Hypoxia and Hypoxemia

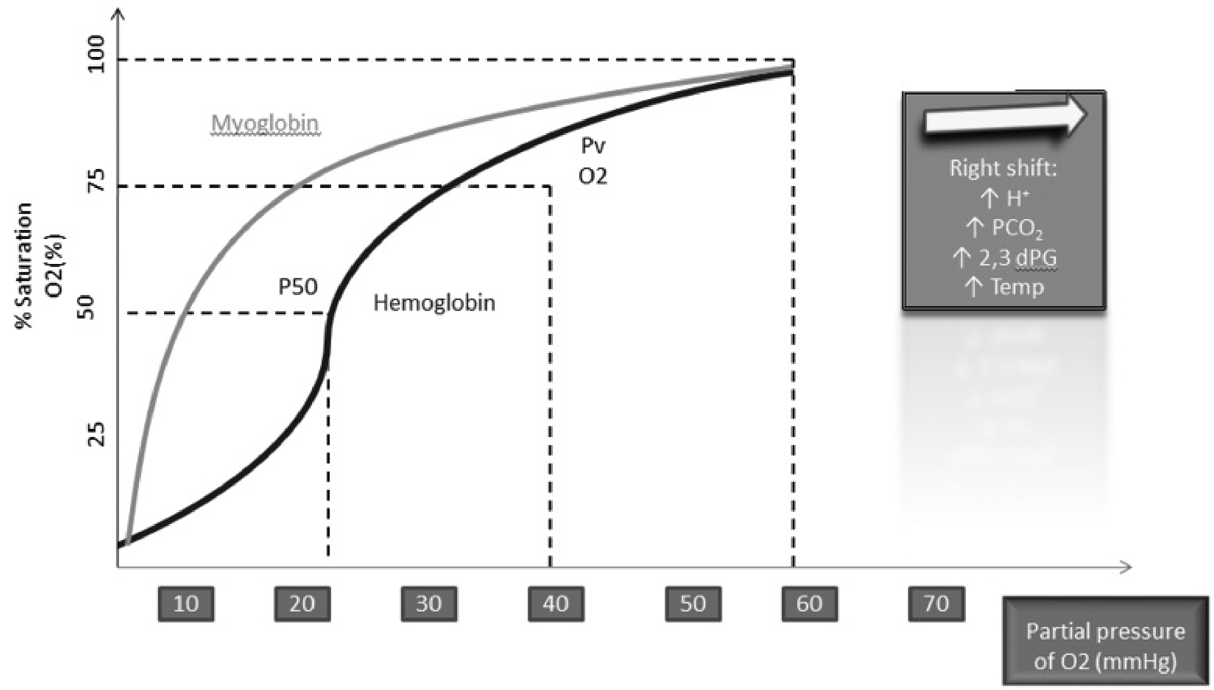
	Definition	Measurable	Examples
Hypoxia	Tissue oxygen needs are unsatisfied.	Decreased oxygen delivery (DO_2), where $DO_2 = CaO_2$ (arterial oxygen content) × Q (cardiac output)	Anemia, low cardiac output, cyanide intoxication, septic shock
Hypoxemia	Oxygen content in the blood is insufficient.	PO_2	Hypoventilation, low FiO_2, poor lung function

The Hemoglobin Dissociation Curve

Few physiological phenomena carry as much significance on a practical clinical level as the oxygen-hemoglobin dissociation curve. Hemoglobin is the major carrier of oxygen to the peripheral tissue. The hemoglobin molecule is formed of the assemblage of a globin and 4 heme molecules. Each of these 4 metalloproteins interacts with 1 molecule of oxygen, leading to the potential uptake of up to 4 molecules of oxygen per molecule of hemoglobin. This complex assemblage is the source of the remarkable property of allosteric cooperation, whereby once a molecule of oxygen combines with a heme group, further binding is favored at the other heme sites, increasing hemoglobin's affinity for oxygen. This also accounts for the sigmoidal form of the oxygen-hemoglobin dissociation curve. For comparison, the oxygen-myoglobin dissociation curve has a hyperbolic form. The monomeric structure of myoglobin precludes allosteric cooperation but allows for a higher oxygen avidity of myoglobin, enabling myoglobin-rich tissues to gain oxygen from hemoglobin (**Figure 1**).

When describing the sigmoidal oxygen-hemoglobin dissociation curve, one can define the P50 as the midinflection point at which the hemoglobin is half in its oxygenated form (oxyhemoglobin) and half in its deoxygenated form (deoxyhemoglobin). Under normal conditions, the P50 of hemoglobin is 27 mm Hg. An increase in P50 equates to a lower affinity of hemoglobin for oxygen and translates into a right-sided shift in the oxygen-hemoglobin dissociation curve. This is seen with increasing P_{CO_2}, 2,3-diphosphoglycerate, and temperature as well as decreasing pH (**Figure 1**).

Figure 1. Hemoglobin and myoglobin oxygen dissociation curves



P50, partial pressure of oxygen at which half of the hemoglobin is in its oxygenated form.

Abbreviation: PVO_2, partial pressure of oxygen in venous blood.

Physiological Characteristics of Arterial Oxygenation

Oxygenation Indexes

Oxygen diffuses from the alveoli to the capillaries according to the concentration gradient. Various conditions can impair this diffusion, and oxygen indexes can reflect the severity of these impairments. An example of such an oxygen index is the alveolar to arterial oxygen gradient, which can be calculated from the computation of the alveolar gas equation.

To measure this gradient, one must first calculate the ideal arterial oxygen tension of $Piao_2$, with the following equation:

$$\begin{aligned} Piao_2 &= FIO_2 \times [PB - PH_2O] - PACO_2/RQ \\ &= 0.21 \times [760 - 47] - [40/0.8] \\ &= 0.21 \times 713 - 50 \\ &= 150 - 50 \\ &= 100 \text{ mm Hg} \end{aligned}$$

where P_B is the barometric pressure at 760 mm Hg; F_{IO_2} is the fraction of inspired oxygen, which at room air is assumed to be 0.21; P_{H2O} is the partial pressure of water at 37°C = 47 mm Hg; Pa_{CO_2} is the partial pressure of arterial carbon dioxide at 40 mm Hg; and RQ is the respiratory quotient at 0.8.

The alveolar to arterial oxygen gradient (P_{AO2}-P_{aO2}) is the difference between the ideal and measured arterial oxygen tensions. This gradient is affected by the patient's age and F_{IO_2}. The gradient is approximately 10 mm Hg in healthy individuals. Conditions such as worsening dead space ventilation, alterations in perfusion, and shunting will lead to an increased gradient.

Other oxygenation indices have been described, particularly in the acute respiratory distress syndrome (ARDS) literature. The most commonly used is the ratio of Pa_{O_2} to F_{IO_2} (the P:F ratio). The P:F ratio owes its popularity in large part to its inclusion in the Berlin criteria for the diagnoses of ARDS. The P:F ratio is generally used as a marker of lung parenchymal ability to transfer oxygen, but this ratio does not account for conditions such as atelectasis or the level of positive end-expiratory pressure (PEEP). The oxygen index was developed to at least partially account for adequacy of ventilation; the oxygen index is calculated as $P_{AW} \times Pa_{O_2} \times 100/F_{IO_2}$, where P_{AW} is the mean airway pressure in cm H_2O.

The Bohr and Haldane Effects on Hemoglobin Dissociation Curve

As discussed previously, the affinity of hemoglobin for oxygen is variable and is influenced by changes in pH and P_{CO_2}. Organisms take remarkable advantage of this property. In what is termed the *Bohr effect*, hemoglobin's affinity for oxygen is decreased in the systemic capillaries where both the concentration of hydrogen ions and P_{CO_2} are increased, which leads to a release of oxygen to tissues where it is needed the most. The oxygen-hemoglobin dissociation curve is therefore shifted to the right.

In the pulmonary capillaries, where both the concentration of hydrogen ions and P_{CO_2} are decreased, hemoglobin's affinity for oxygen is increased, allowing uploading of oxygen onto the heme group. The oxygen-hemoglobin dissociation curve is shifted to the left.

Although less than 10% of carbon dioxide is transported via the hemoglobin, the hemoglobin molecule displays the remarkable property of buffering carbon dioxide at a variable rate. The variability in its buffering capacity is induced by

changes in oxygen tension and is termed the *Haldane effect*.

In a milieu with relatively low oxygen tension, hemoglobin tends to increase its capacity to transport carbon dioxide, leading to a favorable upload of carbon dioxide from the peripheral tissues. Conversely, in a milieu with a higher concentration of oxygen, such as the pulmonary capillary bed, this capacity to carry carbon dioxide is decreased, leading to an off-loading of carbon dioxide in the lungs and thus elimination of carbon dioxide in the respiratory system.

Hemoglobin's variable buffering capacity is mainly attributed to the influence of oxygen on the amino groups of the hemoglobin molecule.

Pitfalls of Interpretation of Arterial Blood Samples

Analysis of blood samples should be performed promptly after sampling. P_{CO_2} increases and Pa_{O_2} decreases the longer a sample sits before analysis. Large air bubbles in the sample will force the Pa_{O_2} readings to drift toward the P_{O_2} of room air. Significant leukocytosis ($>105/\text{mm}^3$), can create a phenomenon called "leukocyte larceny," which lowers the Pa_{O_2} measured in analysis.

CAPNOGRAPHY

Capnography is the graphic display of noninvasive measurements of P_{CO_2}. Capnography is applied to confirm the correct placement of airway devices and can effectively monitor patients' cardiorespiratory condition. Capnometers can be divided into 2 broad categories depending on sampling location: sidestream and mainstream.

In the first category, Raman spectrography exploits the ability of carbon dioxide to scatter light emitted by an argon laser beam. This type of spectrography allows concomitant measurement of the partial pressures of inhalational anesthetic gases and oxygen. Because of size constraints, monitors using Raman spectrography cannot be placed along the breathing circuit; this mandates the usage of sidestreaming and gas sampling. Consequently, if anesthetic gases are administered, a specialized exhaust system is required. Due to gas sampling, this monitor's response can be delayed, but this remains clinically irrelevant unless patients are ventilated at a high rate or with low tidal volumes, such as in the pediatric population.

With sidestreaming, P_{CO_2} readings can be artificially elevated due to a relative

decrease in water vapor tension and/or temperature between the sampling port and the sensor.

With mainstream capnography, infrared spectroscopy exploits carbon dioxide's property to absorb infrared light at a wavelength of 4.3 nm. Falsely elevated P_{CO_2} readings can occur with infrared spectroscopy when high concentrations of either nitrous oxide or oxygen are administered. A high concentration of nitrous oxide leads to a potential confusion of the sensor, because nitrous oxide and carbon dioxide share a similar infrared light absorption profile. A high concentration of oxygen can falsely increase P_{CO_2} readings due to a broadening effect of oxygen on the light absorption. These misreadings can be adjusted by a correcting factor that is built into the monitors. Mainstreaming has the advantage of a quick response time; however, it requires a clear reading channel, which often can be contaminated by secretions and water.

Qualitative capnometers are the second type of mainstream capnographs. These devices use technology based on colorimetric pH-sensitive dyes. As carbon dioxide passes through the device, the carbon dioxide reacts with water and produces carbonic acid. The carbonic acid causes the dye to change from purple to yellow when exposed to P_{CO_2} greater than 15 mm Hg. Qualitative capnometers are small, lightweight, inexpensive and disposable which make them ideal for use in confirming endotracheal tube placement in emergent settings outside of the operating room.

Capnograms can be presented in several ways:

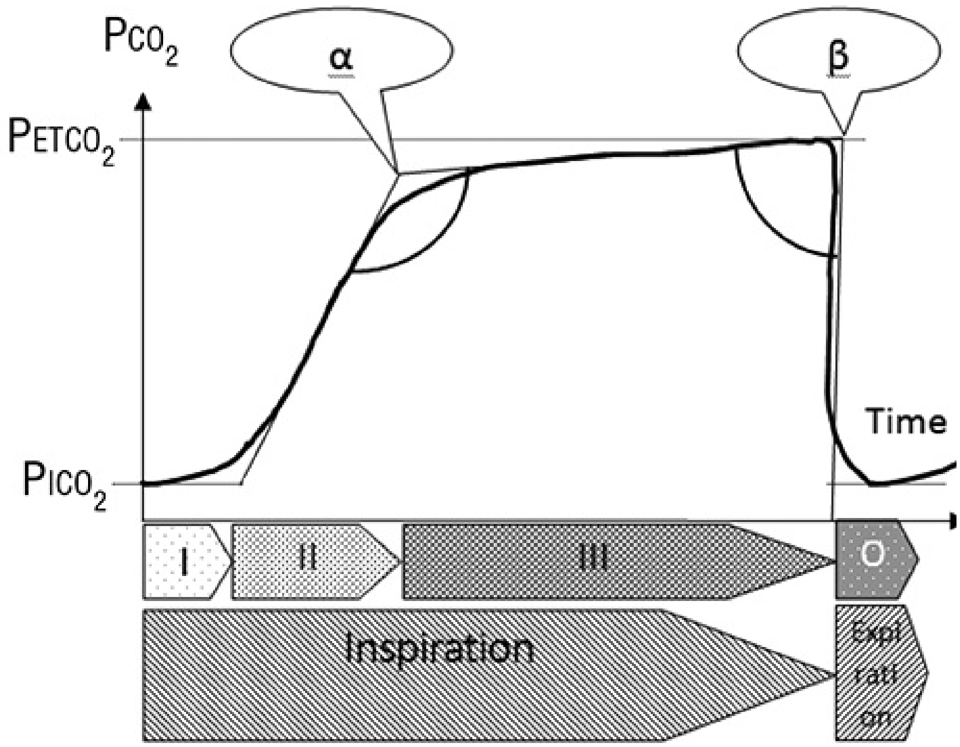
- Time capnography: time is assigned to the x-axis, P_{CO2} is represented on the y-axis. This is the most popular mode of capnography.
- Volume capnography: volume measurements by a pneumotachometer allow the display of P_{CO_2} for each breath on the y-axis with tidal volume on x-axis. In this seldom-used modality, total carbon dioxide production also can be estimated.

Normal Capnograph Waveform

Typical Waveform

Four components make up the typical P_{CO_2} waveform during a respiratory cycle: 3 expiratory phases (I + II + III) and 1 inspiratory phase (0) (**Figure 2**).

Figure 2. Typical capnographic waveform



The waveform depicts the evolution of PCO_2, over a respiratory cycle. During inspiration, 3 phases are depicted: I, II, and III. Expiration is depicted in phase 0. α, angle formed between phases II and III of the capnographic wave form; β, angle formed between phases III and 0 of the capnographic waveform.

Abbreviations: $PETCO_2$, end tidal PCO_2; $PiCO_2$, inspired PCO_2.

- Phase I is initiated at the commencement of the expiratory phase and consists of a low plateau. Phase I represents the washout of the anatomic (and circuit) dead space, which is usually void of carbon dioxide.
- Phase II starts when P_{CO_2} readings increase and follow an S-shaped upstroke curve. Phase II represents the P_{CO_2} readings during a transitional phase. The explanation of this transition between low and high carbon dioxide content derives from the progressive washout of gases originating from the dead space (void of carbon dioxide) by the gases originating from the alveolar spaces (with higher carbon dioxide content). This phase is mostly affected by changes in perfusion.
- Phase III corresponds to a slowly rising, high plateau and represents carbon dioxide drawn from the alveolar units. The slow-rising aspect of the plateau

is explained by the variable rate of diffusion of carbon dioxide from the different alveolar units, as these units display disparate ventilation perfusion ($\dot{V}/\dot{Q}$) ratios. If all units had equal $\dot{V}/\dot{Q}$ ratios, one would observe a flat horizontal plateau. The slope of phase III is mainly affected by increases in airway resistance and alteration in $\dot{V}/\dot{Q}$ ratios. By definition, the partial pressure of end-tidal CO_2 (P_{ETCO_2}) is the uppermost point of the P_{CO_2} observed during phase III.

- Phase 0 begins at the transition between expiration and inspiration and consists of a sharp decline and return to the low baseline. This phase concludes with the initiation of a new inspiration at which point phase I starts again.

The capnograph displays a new P_{ETCO_2} and P_{ICO_2} (or inspiratory P_{CO_2}) for each respiratory cycle.

Angles

The α angle corresponds to the angle formed between the lines representing phase II and III. It is normally approximately 110°. Variations in the α angle are primarily linked to variations in time constants within the different alveolar units and thus overall $\dot{V}/\dot{Q}$ status. Other factors such as cardiac output, airway resistance, and changes in functional residual capacity can also affect the α angle.

The β angle is a straight angle formed between the lines representing phase III and 0 and is commonly affected by rebreathing.

Capnography as a Monitoring Device

Confirmation of Proper Placement of Airway Devices

Confirming the proper placement of an endotracheal tube or a supraglottic device such as a laryngeal mask airway or a Combitube (Covidien, Dublin Ireland) can be challenging in many clinical scenarios. Routine use of capnography may decrease the risk of misplaced airway devices. As per the 2010 American Hospital Association guidelines: “Continuous waveform capnography is the most reliable method of confirming and monitoring correct placement of an endotracheal tube.”

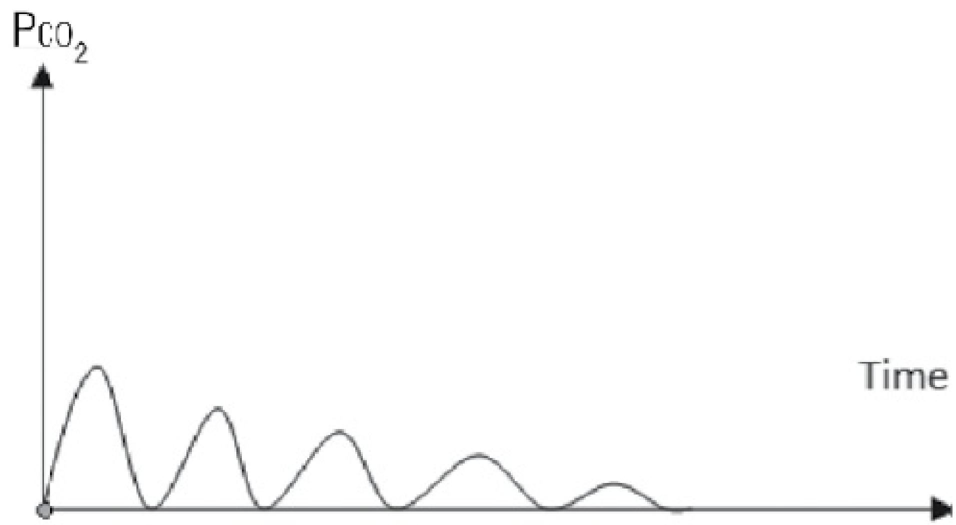
Capnography is a reliable tool and has been shown to be superior (in sensitivity and specificity) to auscultation of the chest after intubation. Capnography allows early recognition of accidental esophageal intubation, preventing a potentially catastrophic outcome.

Semiqualitative colorimetric devices are preferentially used out of the operating room given their low cost, availability, and portability. Quantitative capnographs are preferred in the operating room and ICUs, as these monitors have become ubiquitous and offer more precise and reliable readings. False-positive and false-negative readings have been described in both semiquantitative and quantitative modalities.

Capnography can produce false-negative readings in low-flow states such as cardiac arrest. In such situations, the cardiac output is so low that carbon dioxide transport to the respiratory system is impeded. When P_{CO_2} readings are low, the clinician must quickly determine whether this is attributable to a misplaced endotracheal tube or decreased cardiac output. Alternatively, the reappearance of P_{CO_2} readings is an encouraging sign and suggests effective cardiopulmonary resuscitation. As a result, capnography has been used to monitor the effectiveness of resuscitation and aid in the prognostication of patients with cardiac arrest.

In certain situations, the capnography may mislead the clinician with false-positive P_{CO_2} readings. These situations can occur after esophageal intubation in patients who received prolonged mask ventilation or patients who ingested large quantities of carbonated beverages. Esophageal intubations should still be recognized despite false-positive P_{CO_2} readings, as the capnographs display unique waveforms that usually tend to fade rapidly after 3 to 5 breaths and return to baseline (**Figure 3**).

Figure 3. Capnograph after accidental esophageal intubation



After initial false-positive end-tidal PCO_2 ($PETCO_2$), the PCO_2 decreases to baseline after a couple of breaths.

Surprisingly, despite all the established and potential benefits, no study has clearly demonstrated that capnography improves outcomes in the ICU setting.

Capnography to Monitor Ventilation During Moderate Sedation to General Anesthesia

Undetected hypoventilation and hypoxia carry a heavy burden of severe complications. Both can be easily detected if capnographic monitoring is applied and appropriately interpreted. This is even more compelling in patients undergoing sedation or general anesthesia or those who are in the ICU receiving ventilatory support. Multiple societies, including the American Society of Anesthesiologists and the American Heart Association, support the use of continuous capnographic monitoring in patients undergoing sedation. The American Society of Anesthesiologists guidelines cite such monitoring as part of the standard of care of patients receiving moderate or deep sedation or general anesthesia.

Capnography in Patients Receiving Ventilator Support in the ICU

Should capnography be applied systematically in the ICU, it would enable early detection of complications such as leaks, disconnections, valve malfunction, accidental extubation, and airway obstruction. This would have the potential to enhance patient safety at a relatively low cost. Some have advocated for the adoption of capnography as a standard of care, which would certainly accelerate

this process.

Other Clinical Applications of Capnography

P_{ETCO_2} as a Surrogate for Pa_{CO_2}

Clinicians prefer making informed decisions based on the exact measurement of Pa_{CO_2}. However, this modality entails arterial blood sampling and invasive catheterization of the arterial vasculature if repetitive measurements are needed. These procedures are associated with mechanical, infectious, and thrombotic complications. Capnography has the advantage of avoiding these complications and reducing blood loss, and it is more time- and cost-effective than arterial blood gas (ABG) analysis.

To attest to the veracity of this approximation, a study showed that the majority of samples (90%) had a less than 10 mm Hg difference between the Pa_{CO_2} and P_{ETCO_2}. This study was done in pediatric patients without lung disease.

Estimation of Dead Space Ventilation

The gap between arterial and end-tidal carbon dioxide, termed here $P(a\text{-}ET)_{CO_2}$, is usually negligible in healthy, nonintubated patients: $P(a\text{-}ET)_{CO_2} = 2$ to 5 mm Hg. Multiple cardiac or respiratory pathological conditions can cause an increase in the $P(a\text{-}ET)_{CO_2}$ gap. The interpretation of this gap gives rise to the estimation of alveolar dead space ventilation.

The Bohr equation, first described in 1890, was the first to correlate P_{CO_2} measurements and physiological dead space (sum of anatomic and alveolar dead space). Later, Enghoff simplified the Bohr equation by substituting the partial pressure of alveolar CO_2 (PA_{CO_2}) with Pa_{CO_2} and the mean partial pressure of expiratory carbon dioxide by P_{ETCO_2}. If one divides both ends of the equation by time, this reveals that the ratio of alveolar dead space ventilation divided by total minute ventilation is equal to the ratio of $P(a\text{-}ET)_{CO_2}$ divided by Pa_{CO_2}:

$$V_D/V_T = \frac{P_{ACO_2} - P_{ETCO_2}}{P_{ACO_2}} \equiv \frac{P_{ACO_2} - P_{ETCO_2}}{P_{ACO_2}}$$

where V_D = alveolar dead space volume and V_T = tidal volume.

Physiological dead space volume is determined by measuring the partial pressure of mixed expired P_{CO_2}.

In conditions such as acute pulmonary embolus, one can observe a precipitous decrease in P_{ETCO_2}. If Pa_{CO_2} remains constant, this leads to a significant increase in the $P(a\text{-}ET)_{CO_2}$ gap. A normalization of this gap has been shown to be a positive prognostic sign as it can be seen after reperfusion from thrombolytic therapy or after clot dispersion resulting, for example, from chest compressions. Other examples of processes where the $P(a\text{-}ET)_{CO_2}$ gap is increased include hypovolemia, hemorrhage, and excessive PEEP.

Negative $P(a\text{-}ET)_{CO_2}$ Gap

A negative $P(a\text{-}ET)_{CO_2}$ gap is an uncommon finding. When one is faced with this event, the first step is to verify the validity of the values given from both the capnograph and the ABG analysis machine. The next diagnostic step is to rule out any conditions known to exhibit this finding: patients with low-frequency and high tidal volume ventilation, patients post cardiac bypass, patients who have just exercised, pregnant patients, and pediatric patients.

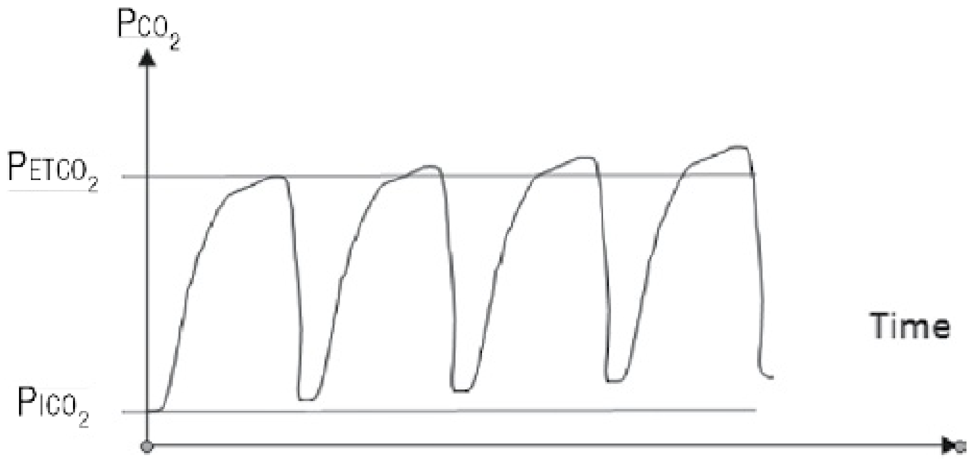
One can observe a negative $P(a\text{-}ET)_{CO_2}$ gap in patients with severe lung disease in whom the carbon dioxide from some pulmonary units is admixed late during the expiratory phase (phase III). This creates an artifactual increase of P_{ETCO_2} and leads to a negative $P(a\text{-}ET)_{CO_2}$ gap.

Examples of Abnormal Capnographic Waveforms

Familiarity with different waveforms allows the clinician to easily detect and diagnose various conditions. The slow increase in baseline P_{CO_2} or P_{ICO_2} can be seen in the following scenarios:

- Carbon dioxide absorbent exhaustion (**Figure 4**)
- Laparoscopic surgery with intra-abdominal insufflation of carbon dioxide and peritoneal absorption
- Rebreathing
- Malfunctioning inspiratory or expiratory valve of the ventilator circuit
- Malignant hyperthermia

Figure 4. Baseline PCO_2 elevation

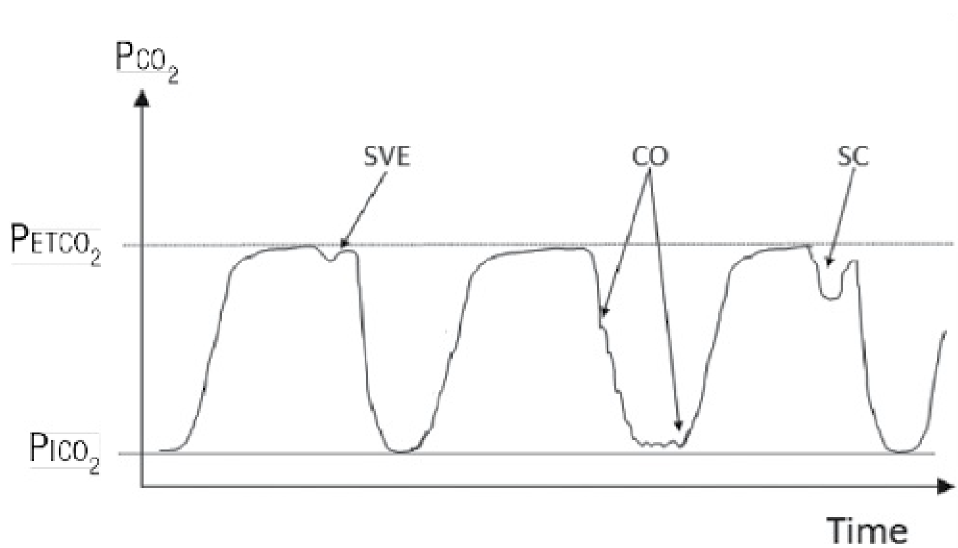


During each breath cycle, $PiCO_2$, which is initially elevated, continues to increase, as does $PETCO_2$.

Abbreviations: $PETCO_2$, end-tidal PCO_2; $PiCO_2$, inspired PCO_2.

Oscillations during the plateau of phase III can be seen in the following scenarios: spontaneous breathing efforts, hiccups, and transmitted thoracic pressure during compression of the chest or abdomen by the surgeon (**Figure 5**). Cardiogenic oscillations can be identified by periodic dips in the end-tidal waveform that occur in unison with the patient's pulse.

Figure 5. Different phases of capnography in phase III



CO, cardiac oscillations, which correlate with heart rate from pulse oximetry or

electrocardiographic monitors.

Abbreviations: $PETCO_2$, end-tidal PCO_2; $PiCO_2$, inspired PCO_2; SC, pressure transmitted during surgical compression of the chest or abdomen; SVE, spontaneous ventilation efforts, hiccups, intermittent diaphragmatic contractions.

Six Miscellaneous Applications of Capnography

Capnography and Alternative Intubations

Capnography has been reported to assist with blind nasal intubation and with confirmation of proper placement of double-lumen tubes. The latter method of confirmation is inconsistent, as some misplacements were overlooked by capnography.

Confirmation of Correct Placement of Percutaneous Tracheostomy

Capnography has been suggested as an adjunct measure to confirm endotracheal placement of a catheter prior to placement of a tracheostomy.

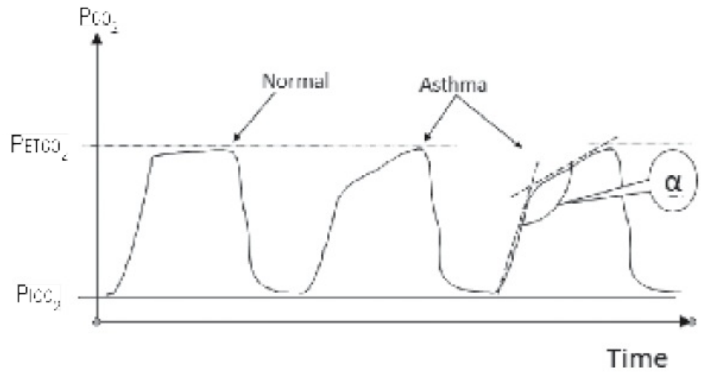
Confirmation of Proper Placement of Feeding Tubes for Enteral Nutrition

Capnography has been suggested as a safe, accurate, and cost-effective method to assist the clinician in placing feeding tubes. When the tip of the feeding tube is advanced, if PCO_2 readings become positive, the tube should be pulled back out of the tracheal tree and the tip of the feeding tube should be redirected posteriorly. This has the potential to avert complications and potentially save costs.

Bronchospasm

A steeper slope of phase III with a greater α angle is an early sign of airway obstruction and possibly bronchospasm, as portrayed in **Figure 6**. The severity of the increases in dead space ventilation can be estimated via the Bohr equation. In spontaneously ventilating patients, the responsiveness of the disease process to bronchodilators can also be monitored via capnography.

Figure 6. Bronchospasm and capnography



Evidence on capnography of bronchospastic exacerbations. Typically, bronchospasm includes an increase in the slope of phase III and an increase in the α angle.

Abbreviations: $PETCO_2$, end-tidal PCO_2; $PiCO_2$, inspired PCO_2.

Acute Respiratory Distress Syndrome

Early in ARDS, an increased $P(a\text{-}ET)CO_2$ gap has been shown to be an independent risk factor for death. As ARDS evolves over time, frequent changes in ventilator settings and recruitment maneuvers may be required. Capnography can assist in making quick and appropriate changes to the ventilator while avoiding ventilator-induced lung injury.

Confirmation of Brain Death

Among other tests, the confirmation of brain death frequently involves an apnea challenge test. This involves confirmation of lack of spontaneous ventilation in the setting of apnea-induced hypercapnia. The level of hypercapnia generally accepted is 60 mm Hg.

Summary of Capnography

Capnographs are ubiquitous and reliable monitors that play a valuable role in the care of critically ill patients. Although rarely used, volumetric capnography gives insight into carbon dioxide production. Time capnography gives insight into various conditions such as $\dot{V}/\dot{Q}$ mismatch, increases in dead space ventilation, and changes in metabolic conditions.

PULSE OXIMETRY

Pulse oximetry is a noninvasive method of measuring hemoglobin saturation (SpO_2) by using a light signal transmitted through tissue. Although pulse

oximetry is one of the most commonly used techniques in the ICU setting, many practitioners do not understand the principles or limitations of this modality.

Principles of Pulse Oximetry

The principle of pulse oximetry is based on the different light-absorbing characteristics of oxyhemoglobin and deoxyhemoglobin at two different wavelengths of light (660 nm [red] and 940 nm [infrared]), and the pulsatile nature of arterial blood flow. A red light-emitting diode (LED) and an infrared LED are located on one side of the probe, and a photodetector is located on the opposite side. The photodetector amplifies only light of alternating intensity. This explains how pulse oximeters detect hemoglobin in pulsating arteries rather than nonpulsatile structures like connective tissue and veins.

Physiological Characteristics

Oxygen saturation is defined as the ratio of HbO_2 to the total concentration of hemoglobin in the blood. When measured by ABG, arterial HbO_2 saturation is referred to as Sa_{O_2}. When measured noninvasively by pulse oximetry, arterial HbO_2 saturation is referred to as Sp_{O_2}.

Efficient oxygen transport relies on the ability of hemoglobin to reversibly load and unload oxygen. The partial pressure of oxygen dissolved in the plasma is measured as the Pa_{O_2}. The oxygen dissociation curve shows the relation between Sp_{O_2} and Pa_{O_2}. An Sp_{O_2} greater than 95% correlates to the normal range of Pa_{O_2}, which is 80 to 100 mm Hg. A Pa_{O_2} of 60 mm Hg or less correlates to an Sp_{O_2} of less than 90% per the dissociation curve.

Equipment and Site Placement

The pulse oximeter consists of a peripheral probe that comes in contact with the patient and a microprocessor unit that displays a waveform, the calculated oxygen saturation percentage, and the averaged pulse rate.

The probe must be placed on a pulsing vascular bed. The machine then reads and averages the waveform values that are detected from the vascular bed. The averaging time is usually 5 to 20 seconds, depending on the machine’s internal setting.

The finger is the most commonly chosen site for probe placement and has a

lower failure rate and more accurate reading compared with earlobe placement. Dark fingernail polish and some synthetic nails can affect readings. Self-adhesive probes are more useful for long-term monitoring or when motion artifact is expected.

The lobe or pinna of the ear can be used with a clip-type probe. Care must be taken when using the ear so that pressure from the clip does not impair perfusion. In circumstances of poor peripheral perfusion, the ear probe performs better than the finger probe.

Forehead probes use reflectance oximetry. With reflectance pulse oximetry, the LED and the photodetector are both on the same side. Light is sent out from the LED, reflects off the tissues, and returns to the photodetector to determine oxygen saturation. The tissue must be well perfused to obtain a strong signal. Compared with the ear or finger, the forehead is less affected by vasoconstriction from cold or poor perfusion.

Accuracy and Advantages

Many studies over the years have shown that there is less than a 3% difference in measured saturation between a pulse oximeter and that of an ABG analysis when the Spo_2 is greater than 70%. Given this repeated accuracy over time, pulse oximetry has been widely used and accepted in various settings. Pulse oximetry also allows practitioners to minimize the use of oxygen support and limit the number of blood gas analyses.

Limitations

Pulse oximetry is a tool in providing patient care, not a replacement for clinical judgement. The measurements provided by pulse oximetry must be placed in the context of the patient, and practitioners must be well versed in its limitations.

Pulse oximeters require an adequate and stable pulse. If peripheral pulses are weak or absent, readings can be difficult to obtain. Patients who are cold but not hypothermic may have vasoconstriction in their fingers and toes that can compromise arterial flow.

The most common cause of inaccurate Spo_2 readings is movement. Movement affects the ability of the light to travel from the LED to the photodetector. Rhythmic movement, such as parkinsonian tremors and seizure activity, as well

as shivering, exercise, and vibrations caused by ground or air transport, can cause problems with detecting saturation and will measure falsely high pulse readings.

Data on the effect of skin pigmentation on pulse oximetry readings are conflicting. Several early studies found that the accuracy and performance of pulse oximeters are affected by deeply pigmented skin. Newer studies refute this argument.

Dyes injected into the venous, arterial, or lymphatic systems can reduce readings by absorbing light. Examples include, but are not limited to, methylene blue, indigo carmine, nitrobenzene, and indocyanine green. Although interference is transient and can last only minutes, injection into the lymphatic system may persist for hours.

Most pulse oximeters cannot differentiate between different forms of saturated hemoglobin. Methemoglobin is an oxidation product of hemoglobin that forms a reversible complex with oxygen and impairs the unloading of oxygen to tissues, thus causing a decrease in Sa_{O_2}. Drugs that can cause methemoglobinemia include benzocaine, prilocaine, nitrobenzene, and dapsone. The Sp_{O_2} decreases by an amount proportional to the concentration of methemoglobin and eventually levels out at 85% for concentrations of methemoglobin greater than 35%. Multiwavelength cooximetry can confirm the diagnosis of methemoglobinemia when there are discrepancies between pulse oximeters and ABG analyses. Similarly, carboxyhemoglobin is formed when carbon monoxide displaces oxygen from iron binding sites in hemoglobin. Hemoglobin's affinity for carbon monoxide is 20 times that of hemoglobin's affinity for oxygen, so hemoglobin carries carbon monoxide in preference to oxygen, thus resulting in the Sp_{O_2} overestimating the Sa_{O_2}.

Summary of Pulse Oximetry

The pulse oximeter, like any clinical monitoring tool, must be used correctly and the results interpreted properly. Pulse oximeters can increase patient safety by alerting the clinician to hypoxia. However, the reading should always be interpreted in association with the patient's clinical condition.

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CHAPTER 19

Acute Respiratory Failure

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Key words: acute respiratory failure, hypoventilation, hypoxia, hypercapnia, respiratory distress

Respiratory failure can be defined as the inability of the respiratory system to effectively carry out oxygenation and ventilation, which involves the intake of oxygen, and elimination of carbon dioxide. In clinical practice, "respiratory failure" is used also to describe a state in which a patient appears to have extreme difficulty breathing. Respiratory failure can be classified into 2 categories based on objective parameters of gas exchange: a PaO_2 less than 55 mm Hg (hypoxemic respiratory failure) or a $PaCO_2$ greater than 45 mm Hg (hypercapnic respiratory failure).

Both classes of respiratory failure can be acute or chronic. In general, patients suffering from acute respiratory failure display signs of distress such as anxiety, use of accessory muscles, and diaphoresis. Once critically low levels of oxygen or dangerously high levels of carbon dioxide are reached, however, the patient becomes encephalopathic or comatose. Signs of respiratory distress on physical examination are a result of the body's effort to overcome acute derangements in oxygenation and ventilation by increasing work of breathing. Chronic respiratory failure, however, often does not present with signs of suffering. Instead, patients are often diagnosed by laboratory values. A low PO_2 on an arterial blood gas reading accompanied by polycythemia in an otherwise comfortable patient indicates a case of chronic hypoxemia, while an elevated PCO_2 with concomitant metabolic alkalosis represents chronic hypercapnic respiratory failure. Often a clinician can quickly deduce the chronicity of respiratory failure by simple calculations; for example, in patients with chronic hypercapnia, every increase in PCO_2 by 10 mm Hg will be accompanied by a decrease in pH of 0.03. In a patient

with acute respiratory acidosis, however, for every increase in P_{CO_2} of 10 mm Hg, the pH will decline by 0.08. If this ratio of P_{CO_2} to pH does not match the values that indicate either acute (10:0.08) or chronic (10:0.03) respiratory failure, then one should consider the possibility of acute-on-chronic hypercapnic respiratory failure.

In addition, providers often have to consider the possibility of mixed states such as acute hypoxemia in the setting of chronic hypercapnia (ie, pneumonia in someone with advanced emphysema). In this scenario, when a patient who has chronic hypercapnia becomes acutely hypoxic, he or she will hyperventilate to raise P_{O_2}. This pseudo-normalizes the P_{CO_2} and accentuates the alkalosis. Thus, in patients with hypoxia who are found to have unexplained metabolic alkalosis, chronic lung disease should be considered.

HYPOXEMIC RESPIRATORY FAILURE

The principal mechanisms of hypoxemic respiratory failure can be separated into intrapulmonary and extrapulmonary factors. The extrapulmonary abnormalities are 2-fold and include low partial pressure of inspired oxygen (P_{IO_2}) (which reduces oxygen content) and low oxygen delivery to the tissues as a result of low cardiac output resulting in tissue hypoxia. The 4 intrapulmonary factors include hypoventilation, shunt, ventilation perfusion ($\dot{V}/\dot{Q}$) inequality or mismatch, and diffusion limitation or abnormality. Low partial pressure of oxygen is only relevant in cases of high altitude, usually above 8,000 feet, and occasionally in patients with poor pulmonary reserve during air travel. The intrapulmonary causes are more common and are discussed at length individually.

Extrapulmonary Causes of Hypoxemia

Low Oxygen Environment

One cause of extrapulmonary hypoxic respiratory failure is low P_{IO_2}, which is uncommon but can result from high-altitude and technical misadventures. In these cases, the alveolar-arterial gradient (P_{AO_2}-P_{aO_2}) is normal and thus lung function is normal.

$$P_{AO_2} - P_{aO_2} = F_{IO_2}(P_{atm} - P_{H_2O}) - P_{aCO_2}/R - P_{aO_2},$$

where F_{IO_2} is fraction of inspired oxygen, Patm is atmospheric pressure, P_{H_2O} is

water vapor pressure, and R is respiratory exchange ratio ($\dot{V}O_2/\dot{V}CO_2$). ($\dot{V}O_2$ and $\dot{V}CO_2$ are oxygen consumption and production, respectively).

Decreases in F_{IO_2} or Patm via travel to altitude will functionally decrease P_{AO_2} and lead to hypoxemia despite normal lung function.

Low Mixed Venous Oxygen

In cases of normal oxygen content, low oxygen delivery states result in tissue hypoxia and generation of lactic acid due to a supply and demand mismatch. Because the tissues are oxygen avid, their oxygen extraction increases. Regardless of the cause of the low oxygen delivery, these states share a common end point: low oxygen saturation of the blood returning to the lungs. In normal lungs, this blood can be rapidly reoxygenated, but in states where there is already some impairment of lung oxygenation, blood can leave the lungs not fully oxygenated. Thus, low cardiac output can sometimes affect arterial oxygenation.

$$
\begin{aligned}
DO_2 &= \text{Cardiac Output} \times \text{Carrying Capacity} \\
&= \text{Cardiac Output} \times [(\text{Hb} \times \%\ \text{Saturation of Hb} \times 1.34] + PaO_2 \times 0.003)
\end{aligned}
$$

where DO_2 is oxygen delivery, Hb is hemoglobin (g/dL), 1.34 is the amount of oxygen carried by hemoglobin (mL/g), and ($PaO_2 \times 0.003$) is the amount of oxygen dissolved in plasma. Carrying capacity is equivalent to oxygen content.

Intrapulmonary Causes of Hypoxemia

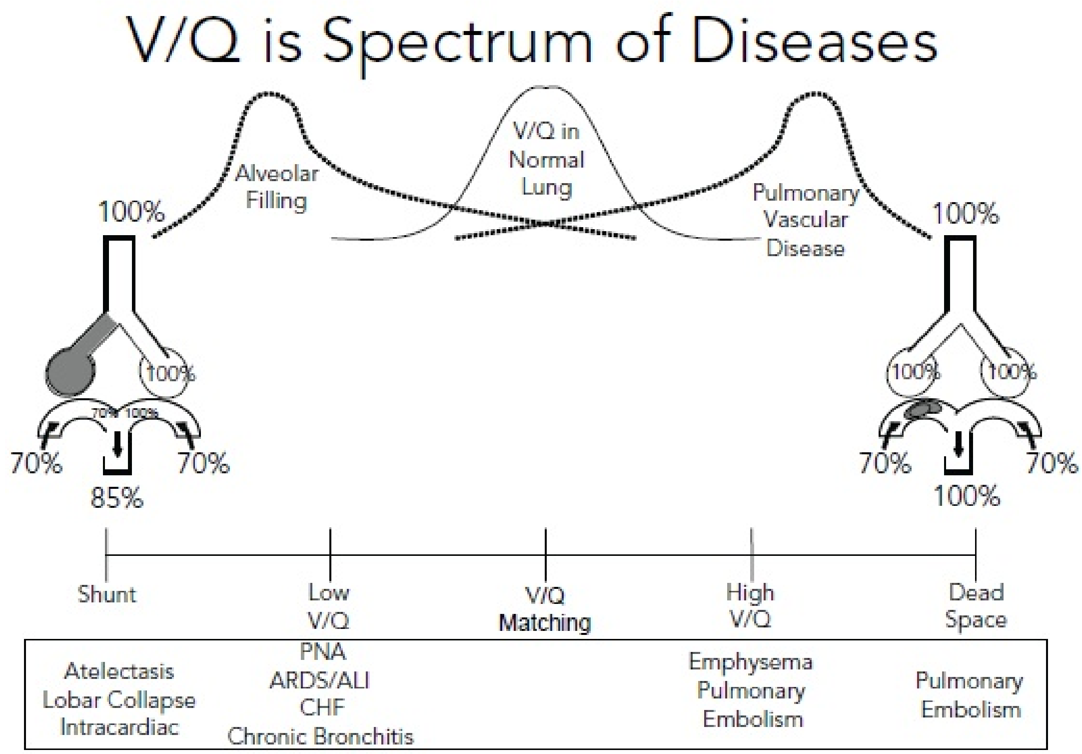
Shunt

Shunt is characterized by perfusion without accompanying ventilation. Hypoxemia due to shunt is not reversible with increases in F_{IO_2}. Shunts can be structural or physiological. Structural shunts are either intracardiac or intrapulmonary in nature. In either case, mixed venous blood from the right side of the heart enters the left atrium without contacting alveolar gas. Intracardiac shunts are direct right-to-left communications that include patent foramen ovale, patent ductus arteriosus, and atrial or ventricular septal defects. Intrapulmonary shunts include abnormal connections between pulmonary arteries and pulmonary veins such as arteriovenous malformations. Patients are often screened for shunts

by contrast echocardiography, in which air bubbles injected into the venous circulation arrive at the left atrium, indicating that they have not been filtered by the lung's capillary bed. The timing of arrival of the bubbles to the left atrium helps to determine whether the shunts are intracardiac or intrapulmonary in nature, the former arriving within 1 to 3 cardiac cycles and the latter typically within 6 to 8 cycles.

Physiological shunting is also commonly found in states of dense alveolar filling or collapse, such as atelectasis, pneumothorax, central airway obstruction, or compressive atelectasis due to abdomen or pleural effusions. In these conditions, hypoxic vasoconstriction reduces much of the blood flow through the nonaerated lung zones but not completely, thus leaving areas of perfusion without ventilation. Alveolar filling processes caused by pneumonia, acute respiratory distress syndrome (ARDS), alveolar hemorrhage, and congestive heart failure usually affect the lung parenchyma in a heterogeneous fashion and have elements of both shunt and ventilation perfusion mismatch. Often hypoxic patients are on a spectrum of disease between shunt and $\dot{V}/\dot{Q}$ mismatch. At the extremes of this spectrum are shunt ($\dot{V}/\dot{Q} = 0$ where ventilation, the numerator, approaches zero and perfusion is unopposed) and dead space ($\dot{V}/\dot{Q}$ = infinity where perfusion, the denominator, approaches zero) (**Figure 1**).

Figure 1. Spectrum of diseases involving $\dot{V}/\dot{Q}$



Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; PNA, pneumonia, $\dot{V}/\dot{Q}$, ventilation/perfusion ratio.

Ventilation Perfusion Mismatch

This is probably the most common cause of hypoxemic respiratory failure. Optimal gas exchange is based on maximal matching of ventilation and perfusion, that is, a $\dot{V}/\dot{Q}$ ratio equal to 1. In a healthy person the ventilation perfusion ratio is not uniform in the lung, but the summation of the 300 million alveoli in a normal distribution around a $\dot{V}/\dot{Q}$ ratio equal to 1. In disease states, regional mismatching of ventilation to perfusion within the lung leads to ineffective gas exchange. This can occur either in the form of regional vascular dropout, such as in emphysema or a large pulmonary embolus leading to a high $\dot{V}/\dot{Q}$ process (nearing dead space physiology, which leads to hypercapnia), or in the form of a patchy alveolar filling process leading to a low $\dot{V}/\dot{Q}$ state (nearing but not equaling shunt and producing hypoxia). Some of the most common conditions associated with abnormal $\dot{V}/\dot{Q}$ matching are described in more detail next.

Pneumonia

Pneumonia is inflammation and infection of the lower respiratory tract and

alveoli due to either viruses or bacteria. Classically, pneumonia presents with a clinical history of increasing cough, purulent sputum, fevers, dyspnea, and focal examination findings. Unfortunately, the sensitivity of a clinical diagnosis ranges from 50% to 80%. The lungs are constantly exposed to environmental pathogens and particulate matter (daily alveolar ventilation of 7,000-10,000 L/d). Pneumonia represents the ability of a particular virus or bacteria to overcome the natural defense mechanisms of the lung, including barrier functions, mucociliary clearance, and the innate and the adaptive immune response. A breach in these defense mechanisms can be related to the virulence of organism, the size of the inoculum (eg, aspiration event), mucociliary clearance disruption (as in ciliary dyskinesia), or a deficiency particular to the individual patient (eg, immunoglobulin G deficiency, HIV, *CFTR* gene mutation). When defense mechanisms are disrupted, the lower airways and alveoli begin to fill with purulent material over time. This material is composed of bacteria and cells, both alive and dead, and exudative fluid resulting from disruption of basement membranes and cellular tight junctions. Eventually, the disruption in alveolar ventilation reveals itself as hypoxemia due to low $\dot{V}/\dot{Q}$ and in extreme areas of shunt ($\dot{V}/\dot{Q} = 0$).

Cardiogenic Pulmonary Edema and Congestive Heart Failure

Pulmonary edema is characterized by fluid accumulation in the interstitium and alveolus due to disruption of the process that regulates the direction and rate of fluid exchange. Classically, this accumulation of fluid outside the capillary is described as either cardiogenic, due to problems at the level of the left heart leading to changes in capillary hydrostatic changes, or noncardiogenic, due to oncotic pressure changes and/or capillary permeability changes. In cardiogenic pulmonary edema, the final common pathway is an elevated left atrial pressure with ensuing elevations in pulmonary venous hydrostatic pressure within the capillary bed. This elevation in left atrial pressure may reflect valvular disease like mitral stenosis, diastolic relaxation abnormalities due to ischemia, or chronic hypertension or systolic dysfunction.

The causes of hypoxemia are multifactorial for patients with congestive heart failure. Early in the course, congestive heart failure is represented by primarily interstitial fluid, and thus diffusion abnormality may be the primary driver of hypoxemia. This interstitial fluid also can promote areas of low $\dot{V}/\dot{Q}$ via 2 mechanisms. First, accumulation of fluid (including pleural effusions that put the diaphragms at a mechanical disadvantage) causes a decrease in lung compliance leading to regional declines in ventilation. Second, as fluid continues to enter the

interstitium, the airways surrounded by this interstitial fluid become narrowed, leading to a further decline in ventilation. Clinically, this narrowing of airways presents as the classic cardiac wheeze on physical examination. As the disease progresses, alveolar flooding takes place and areas with low $\dot{V}/\dot{Q}$ convert to shunt physiology and progressive hypoxemia.

Noncardiogenic Pulmonary Edema and Acute Respiratory Distress Syndrome

The initial unifying feature of ARDS is increased capillary permeability due to either direct lung injury or systemic inflammation. The common end point is diffuse damage to the alveolar-capillary membrane. This leak of protein and fluid progresses pathologically and is represented by the appearance of the classic hyaline membranes lining the alveoli. It then is followed by what is described as the proliferative phase of injury with fibrin deposition and inflammatory cell infiltration. The final stage of this disease results in fibrosis of the alveolar ducts, alveoli, and interstitium. The clinical criteria for ARDS include acute onset of bilateral infiltrates (within 1 week) without evidence of cardiogenic pulmonary edema (by echocardiogram) with a PaO_2 to FIO_2 ratio (P:F) of less than 300. ARDS is graded in severity by the P:F ratio (mild being P:F 200-300 mm Hg, moderate 100-200 mm Hg, and severe <100 mm Hg).

The hypoxemia associated with ARDS is the result of several elements. In the early phase of increased permeability and fluid extravasation; hypoxemia initially is driven by low $\dot{V}/\dot{Q}$. As this progresses, data from computed tomography scans suggest that dependent portions of the lung become less ventilated and eventually atelectatic while the more anterior portions of the lung become overdistended. This is due to chest wall restrictions; in a supine patient, posterior ribs pressed against a bed cause decreased compliance, and gravity causes increased pooling of fluid and exudate along posterior aspects of the lung, while the anterior ribs and sternal unit allow chest wall expansion anteriorly and air inflates the area of the lung with the least resistance. Interventions like recruitment maneuvers and high positive end-expiratory pressure (PEEP) may improve the P:F ratio but have not consistently been shown to improve mortality rate.

Treatment of ARDS is guided by 2 principles: (1) reducing alveolar collapse through the use of PEEP and (2) using small tidal volumes to limit damage to open lung segments and not overdistend them. In 2001, in a randomized controlled trial of 861 patients with ARDS, the ARDS Network demonstrated

that mechanical ventilation with low tidal volumes (6 mL/kg of ideal body weight) and plateau pressures less than 30 mm Hg produced a 9% reduction in mortality (from 40% to 31%). Other clinical and animal studies have demonstrated that high peak pressures and high tidal volumes are associated with inflammation in lung and serum, leading to injury to the lung and other distant organs. The goal of ventilation in ARDS is to reduce ventilator-induced lung injury, which comes in the form of barotrauma, volutrauma, atelectrauma, and oxygen toxicity. The ideal settings allow the alveoli to remain open without repeat episodes of collapse, with driving pressures that allow for distention between the lower and higher inflection points on the compliance curve of the lung. Strategies to determine the ideal settings include plotting compliance curves and using esophageal balloons to determine true transpulmonary pressure especially in settings of poor chest wall compliance (eg, obesity).

Diffusion Abnormalities

Diffusion is the main method of gas movement in the distal small airways and of gas exchange in the alveoli. Gas exchange is dependent on several factors: (1) an intact alveolar-capillary membrane, (2) the partial pressure of the gas diffusing between the 2 compartments, and (3) the time that individual red blood cells spend in the capillary bed to allow for complete gas exchange at the interface. The rate of oxygen binding to the hemoglobin molecule is nonlinear and increases with each individual oxygen molecule bound. This maintains the maximal pressure gradient between the oxygen in the alveoli and the partial pressure of oxygen dissolved in plasma, allowing for very efficient transfer of oxygen across the alveolar-capillary membrane. The time that a red blood cell spends in the capillary bed in a normal patient is 2- to 3-fold that is required to achieve complete uploading of oxygen. Consequently, diffusion is rarely impaired.

Diseases that classically affect diffusion include pulmonary hypertension and interstitial diseases. The alveolar-capillary membrane is so efficient and redundant that patients are generally not hypoxemic unless they exert themselves or until very late in the disease process. Hypoxemia with exertion can be explained in part by a decreased time for diffusion to occur across the alveolar-capillary membrane attributable to increases in flow through the capillary bed. The normal response to exertion is to increase cardiac output and recruit pulmonary vascular units, thus causing a decline in pulmonary vascular resistance. Patients with pulmonary hypertension or interstitial disease are unable to recruit pulmonary vascular units; thus, flow rates through the capillary

bed increase, leading to a decrease in time for uptake of oxygen in the capillary unit.

Hypoventilation

This can be considered the final common pathway for all causes of respiratory distress and is discussed in more detail in the following section.

HYPERCAPNIC RESPIRATORY FAILURE

If one considers the lungs as a pump that moves oxygen in and carbon dioxide out, hypercapnic respiratory failure can be viewed as pump failure. Under normal conditions, the level of P_{CO_2} varies directly with minute ventilation (MV), and the hallmark of hypercapnic respiratory failure is an elevated P_{CO_2} seen on arterial blood gas studies. Sometimes, under abnormal conditions, the relationship between the observed MV and the P_{CO_2} can become uncoupled and even move in the opposite direction, as is seen in states of increased dead space fraction or ineffective breathing. Thus, hypercapnic respiratory failure can be divided into 2 categories: states of low MV and states of high dead space. Although many conditions lead to both forms of respiratory failure, this section of the chapter is limited to acute conditions.

Hypercapnic Respiratory Failure From States of Low Ventilation

Secondary Hypoventilation (Fatigue)

Perhaps the most common reason for an elevated P_{CO_2} in a patient with respiratory failure is fatigue brought on by excessive demand. Anything that causes acute hypoxia or acute acidosis will increase MV in a normal person. The demands can exceed the person's ability to sustain this level of ventilation, and respiratory muscle fatigue will begin. Fatigue can occur quickly or happen slowly over time. Testing blood gases to assess for metabolic acidosis or calculating an alveolar-arterial gradient can be helpful to distinguish patients who have primary hypoventilation (low P_{O_2}, high P_{CO_2}, normal alveolar-arterial gradient) from those who have fatigue due to compensation for primary hypoxia (low P_{O_2}, high P_{CO_2}, elevated alveolar-arterial gradient) or a metabolic acidosis.

Another important factor is a patient's respiratory muscle strength. Those who are strong and healthy may be able to sustain long periods of hypoxia or acidosis

without fatigue. Those who are not strong or who have underlying chronic conditions that limit ventilation, such as chronic obstructive pulmonary disease (COPD), chest wall abnormalities, or neuromuscular diseases, may tire rapidly and with minimal new demands. Many episodes of respiratory failure are of mixed cause, with fatigue usually being the second component. It is important to look past the hypoventilation and determine what may have precipitated it.

Primary Hypoventilation

The causes of primary hypoventilation are so numerous that they are best considered in broad categories and not as individual diseases or conditions. Most conditions that cause hypoventilation generally cause chronic respiratory failure, and thus a clue to their presence often lies in evidence of chronic hypoventilation such as elevated bicarbonate or a compensated respiratory acidosis. A useful way to approach a patient with an unexplained primary hypoventilation is to consider, from start to finish, the pathways and mechanisms by which we breathe.

Central Nervous System Disorders

The central nervous system (CNS) initiates and regulates both the rate of breathing and the drive to breathe. Thus, anything that can affect the CNS can influence ventilation. Perhaps the most common culprits in acute respiratory failure are sedating drugs such as opiates, ethanol, or benzodiazepines. Additionally, injury to the brain and brainstem can depress respiration, the most common of such injuries being traumatic brain injury, cerebral edema, anoxic brain injury, intracranial hemorrhage, and stroke. When these disorders affect breathing, the level of consciousness almost always decreases.

Motor Neuron Problems

The spinal cord is a common site of injury that can lead to hypoventilation. Injury to the upper cervical cord (above C3) can eliminate all ventilation through paralysis of the diaphragm and the intercostal muscles. Injuries to C3-C5 will have variable effects on respiration depending on the amount of injury to the spinal cord at that level. Injuries below C5 will paralyze only the intercostal muscles but will allow diaphragmatic breathing. Injury is usually in the form of trauma but can also occur through infections, stroke, or tumor. Diseases such as amyotrophic lateral sclerosis and transverse myelitis can paralyze or weaken the muscles of respiration at the level of the spinal cord.

Peripheral nerve dysfunction can cause acute respiratory failure but is less

common. Following trauma or thoracic surgery, phrenic nerve injury can lead to respiratory failure and can be difficult to diagnose through routine examination and radiological studies. Several types of progressive paralyses can lead to respiratory failure, such as Guillain-Barré syndrome and myasthenia gravis. Patients can acquire a neuromyopathy from critical illness that can be severe enough to compromise respiration, but this more commonly manifests as failure to wean from mechanical ventilation than it does as a primary cause of respiratory failure.

Neuromuscular blocking agents can cause prolonged peripheral nerve dysfunction. This is often a result of impaired clearance of the drug or incorrect dosing but can be idiopathic. Toxins also can cause respiratory muscle dysfunction. Although uncommon in developed nations, tetanus, botulism, and organophosphate poisoning are common causes of respiratory failure in the developing world.

Most causes of neuromuscular dysfunction cause chronic hypoventilation. Their role in acute respiratory failure is attributable more to the fact that these patients have limited respiratory reserve and thus small insults such as medications or fatigue can have a disproportionately large impact. The most common scenario by which these conditions lead to acute respiratory failure is dysfunction of the muscles of the upper airway, which can precipitate aspiration and pneumonia.

Respiratory Muscle Dysfunction

Respiratory muscle dysfunction can occur in 2 ways. On the cellular level, muscle dysfunction most commonly occurs through malnutrition, fatigue, or electrolyte disorders such as hypophosphatemia or hypokalemia. Muscle dysfunction can occur also through congenital diseases such as muscular dystrophy or mitochondrial myopathies. Isolated primary muscle dysfunction rarely causes acute respiratory failure but in times of distress contributes by limiting a patient's reserve. Some mitochondrial myopathies can worsen in times of malnutrition or stress and cause precipitous declines in strength. Respiratory muscle dysfunction on a larger scale is generally grouped with chest wall disorders as a cause of respiratory failure.

The second way that respiratory muscle function can be impaired is through disorders of the chest wall and its mechanics. These are rarely the sole cause of respiratory failure but can be a secondary contributor. Common acute conditions include burns and trauma, while kyphoscoliosis is a well-known chronic

condition that results in hypercapnia. Increasingly, clinicians are seeing obesity-related conditions that can either mimic (obstructive sleep apnea) or exacerbate (obesity hypoventilation syndrome) acute respiratory failure.

Hypercapnic Respiratory Failure From Increased Dead Space

Respiratory failure from increased dead space is usually related to air trapping from an obstructive lung disease but can sometimes come from pulmonary vascular conditions such as pulmonary embolism. As the dead space fraction increases, it negatively affects breathing in 2 ways. First, it requires more MV (and thus more work) to accomplish the same amount of oxygenation. Second, for a fixed MV, alveolar ventilation decreases as dead space increases.

In obstructive airway disease like COPD, this process can create a downward spiral into respiratory failure. Some initial insults (such as a pneumonia) result in new or worsening hypoxemia. The response is to increase MV by raising the respiratory rate. Higher respiratory rates result in shorter expiratory times and thus more air trapping. As air trapping increases dead space, ventilation becomes less efficient and alveolar ventilation is further reduced. Conversely, the initial insult could be something that increases airway obstruction, such as bronchospasm.

For patients with end-stage lung diseases like COPD or pulmonary fibrosis, any cause of tachypnea can precipitate the decline. As one breathes faster, tidal volumes shrink as muscle fatigue sets in. Since there is a fixed amount of anatomical dead space in the lung from the large airways, shallow breathing alone increases the dead space fraction and thus decreases the alveolar ventilation. This ineffective ventilation can precipitate respiratory failure in patients with advanced lung diseases.

Conditions of the pulmonary vasculature can increase dead space as well. In cases of large pulmonary emboli, all lung distal to the clot becomes dead space. This is reflected in the clinical observation that many patients with pulmonary emboli feel severe dyspnea and yet have little hypoxia.

OTHER CAUSES OF RESPIRATORY FAILURE

One important cause of respiratory failure that should not be overlooked is upper airway obstruction. The obstruction can come from a foreign body such as food but also can result from conditions such as upper airway tissue edema (tongue,

epiglottis, larynx), blood clots from upper airway bleeding, and acute vocal cord dysfunction. Patients with decreased mental status or poor cough are particularly susceptible to these conditions. Before any other efforts are made to treat or diagnose an episode of acute respiratory failure, the airway needs to be evaluated for patency.

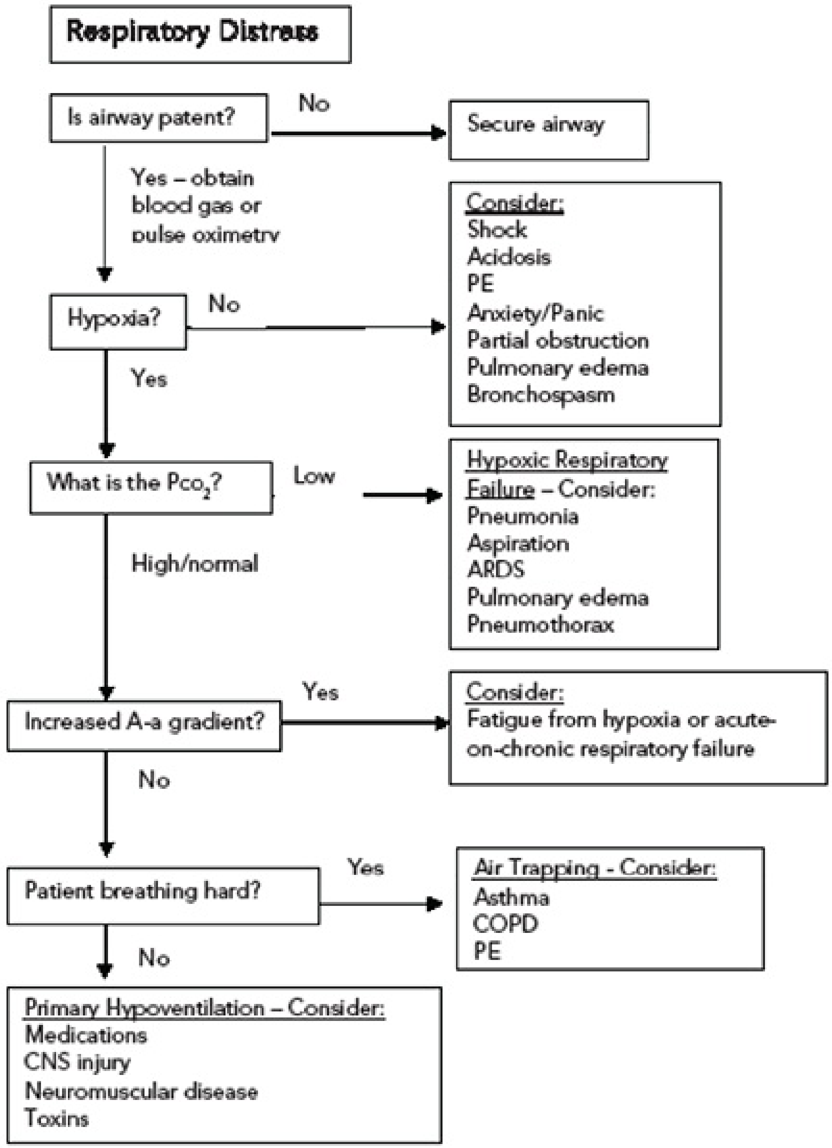
Several conditions can mimic respiratory failure by increasing sensations of dyspnea or inducing tachypnea. In some patients, these conditions can lead to respiratory failure through fatigue. One of the most common is a metabolic acidosis that causes a compensatory increase in the MV. When an initial workup reveals normoxia and no clear pathological condition in a patient with respiratory distress, acidosis should be considered. Psychiatric conditions, such as panic attacks or anxiety, can also mimic respiratory failure. Vocal cord dysfunction syndrome involves paradoxical vocal cord motion associated with psychosocial disorders that can mimic asthma and respiratory distress. In rare cases, it can precipitate true respiratory failure.

GENERAL APPROACH TO THE PATIENT WITH RESPIRATORY DISTRESS

A systematic approach is recommended for the assessment of a patient with respiratory distress with emphasis on the prompt establishment of adequate oxygenation, control of the airway, and ventilatory support if needed. Once these are established, efforts should focus on establishing the cause of the respiratory failure to guide treatment.

It is important to establish 3 simple facts at the outset. Is there a patent airway? Is the patient normoxic or hypoxic? Is the patient hemodynamically stable? A history of the event and a thorough physical examination should be obtained. Often, this alone will provide the diagnosis. An arterial blood gas study can be helpful in distinguishing primary hypoventilation from fatigue or acidosis and can provide a rough assessment of the patient’s true effective MV. An example of a systematic approach to evaluating a patient with respiratory failure based on a few key pieces of data can be found in **Figure 2**.

Figure 2. Evaluation of the patient with respiratory distress



Abbreviations: ARDS, acute respiratory distress syndrome; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism.

SUMMARY

The most important concerns when treating a patient with respiratory failure are to first secure the airway and stabilize the patient and then to consider all possible causes. Anchoring bias or being focused on a specific possible cause may prevent one from identifying the true cause. A large percentage of respiratory failure events involve multiple concurrent insults such as pneumonia and bronchospasm or depressed CNS and aspiration. Awareness of all pathological processes will greatly enhance the treatment of the event.

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CHAPTER 20

ICU Management of Obstructive Airway Disease

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Key words: acute respiratory failure, asthma, auto–positive end-expiratory pressure, chronic obstructive pulmonary disease, helium-oxygen mixture, noninvasive mechanical ventilation

DEFINITIONS

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive lung diseases characterized by shortness of breath, chest tightness, increased respiratory rate with a prolonged expiration, contraction of accessory muscles, and focal or diffuse wheezing. When obstruction is most severe, wheezing may not be present given the severe limitation of flow. Associated large intrathoracic pressure swings cause an accentuated pulsus paradoxus.

Diagnosis of obstructive lung disease is typically made by pulmonary function testing. The hallmarks of both asthma and COPD are the following:

- Reduction in forced expiratory volume in the first second of expiration (FEV_1) out of proportion to the reduction (if present) in forced vital capacity with categorization of severity based on degree of FEV_1 reduction
- Increased residual volume and/or ratio of residual volume to total lung capacity consistent with air trapping

When spirometry is not practical, the use of peak expiratory flow rate (PEFR) is potentially valuable. Because it occurs at the initiation of forced expiration, PEFR is a reliable and reproducible measurement. In adults, a PEFR less than 125 L/min implies severe obstruction. Such obstruction also can be predicted by a reduction of more than 30% in baseline PEFR.

In asthma, both symptoms and spirometric abnormalities are typically entirely reversible. However, there is increased evidence, particularly in older patients and those with long-standing asthma, of asthma-COPD overlap syndrome. Asthma typically involves both large and small airways and is characterized by eosinophilic inflammation and predominance of type 2 helper T cells, whereas COPD is characterized by neutrophils and CD8 helper cells. Asthma has bimodal presentations in childhood and in middle age and is seen more often in city dwellers of African American and Hispanic origin. COPD is more common in city dwellers, although occupational sources and air pollution may also be factors. Asthma-COPD overlap syndrome has a combination of these factors, is more common in middle age, and is often associated with gastroesophageal reflux disease, congestive heart failure, and obesity.

EPIDEMIOLOGICAL CHARACTERISTICS

The prevalence of asthma is increasing, affecting an estimated 26 million Americans. The incidence is highest in those younger than 18 years, in females, and in those of mixed race, particularly of African American or Native American origin. Rates of death attributable to asthma, as well as clinic and emergency department visits, have increased since 2000. Approximately 1.8 million visits to an emergency department were due to asthma in 2011, and 3,600 deaths were attributed to asthma in 2013, the majority in African Americans older than 18 years. From 2001 to 2009, asthma death rates in the United States decreased from 15 deaths per million to 10.5 deaths per million. Asthma currently ranks as the 35th most common cause of death in the United States.

COPD is typically a disease of smokers, although it may be caused by occupational exposures and second-hand smoke and is increased by genetic predispositions such as α_1-antitrypsin deficiency. Death rates from COPD in US men have continued to decline since the late 1990s, and this is attributed to reduced rates of tobacco use. In 2010, the rate of death from COPD in men was 47.6 in 100,000. In women, however, rates of COPD and death due to COPD continue to increase, and these patterns are also commensurate with tobacco use. As of 2010, COPD rates of death in women were 36.4 in 100,000. COPD ranks nationally as the fourth leading cause of death, and unlike the other 5 leading causes of death (heart disease, cancer, stroke, unintentional injuries, and diabetes mellitus), COPD did not show a reduction in death rates from 1969 to 2013.

ASTHMA

Findings With Increased Severity

Non-MB-creatine phosphokinase can be increased in people with acute asthma who perform strenuous muscle activity. Severe asthma can cause right-sided heart strain on electrocardiogram. Arterial blood gases initially show acute respiratory alkalosis with normal oxygenation. Subsequently, despite hyperventilation, oxygenation declines, and with ventilatory muscle fatigue, Pa_{CO_2} rises to normal and then increases pathologically. Normal Pa_{CO_2} in a distressed asthmatic patient is an ominous sign. Other acid-base disturbances may be present at the time of admission to the ICU and include the following: (1) a compensatory non–anion gap metabolic acidosis driven by renal sources in patients who have been chronically hyperventilating and (2) a lactate-induced anion gap metabolic acidosis with sources of lactate being respiratory muscle production, the direct cellular effect of aggressive β-agonist therapy, and decreased perfusion of the liver (the organ responsible for lactate clearance).

Oxygenation and Ventilation

Almost all of the hypoxemia in asthma is due to a low pulmonary ventilation-perfusion ratio and is responsive to oxygen therapy. Patients with severe asthma usually can be oxygenated easily with oxygen concentrations of 28% to 35%. Asthma is a primarily ventilator defect. Typically, derangements in Pa_{CO_2} are more profound and are recognized earlier than those of Pa_{O_2}. This is collectively the result of bronchoconstriction, mucous plugging, increased work of breathing, and air trapping with increased dead space.

Drug Therapy

β-Adrenergic Therapy

Inhaled β_2-selective agonists are the cornerstones of treatment for acute asthma. Fears that frequent use of β-agonist inhalation therapy before hospital presentation might make subsequent use of these agents less effective are unfounded. β_2-Selective agents should be delivered by inhalation at larger and more frequent dosing intervals because of decreased deposition at the site of action (low tidal volumes and narrowed airways), high inspiratory frequencies and flow rates, alteration in the dose-response curve, and altered duration of activity. According to recommendations from the US National Institutes of Health (NIH), initial therapy in acute asthmatic patients is 2.5 to 5.0 mg of

nebulized albuterol every 20 minutes for 3 doses. Options also include the use of levalbuterol, bitolterol, or pirbuterol.

The Canadian Association of Emergency Physicians, American Lung Association, and American Thoracic Society recommend 5 mg of nebulized albuterol every 15 to 20 minutes for 3 doses for the initial management of severely ill asthma patients (FEV_1 or PEFR <40% of predicted).

According to the National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, albuterol delivery by a pressurized metered-dose inhaler (MDI) with a spacer, at a dose of 4 to 8 puffs every 20 minutes for 3 doses and then every 1 to 4 hours as needed, is at least equivalent to small-volume nebulizer delivery. Studies in the emergency department suggest that the MDI method may be more effective than nebulization, because the drug is delivered in a shorter period of time (1-2 minutes). This regimen requires patient cooperation and proper technique.

Tachycardia and hypokalemia are common side effects of β-agonist therapy. β-Agonists can increase the risk of ventilator-associated pneumonia in intubated ICU patients. Hypokalemia-induced dysrhythmias can occur because inhaled β-agonists decrease serum potassium; this occurs more often with concomitant steroidal and diuretic medications.

Subcutaneous β-agonist therapy (epinephrine, terbutaline) has a disadvantageous therapeutic-toxicity ratio when compared with inhaled β_2-selective agonist therapy. IV β-agonist therapy, in general, has no advantage over aggressive inhaled therapy and may produce increased toxicity.

For asthmatic patients who are at imminent risk of respiratory arrest, a combination of inhaled and subcutaneously administered β-agonists is recommended. The subcutaneous epinephrine dose for adults is 0.3 to 0.5 mL of a 1:1,000 dilution, depending on age and weight; this dose can be repeated thrice in the initial management every 15 minutes. Terbutaline is the parenteral agent of choice in pregnancy. β_1-Adrenergic stimulators are given subcutaneously and should be avoided in elderly patients and in those with cardiac diseases.

Corticosteroids

Corticosteroids are an essential part of in-hospital asthma therapy. The NIH expert panel recommendation is IV methylprednisolone 120 to 180 mg/d in 3 or 4 divided doses for 48 hours in patients admitted to the hospital, with tapering

and oral formulations (prednisone) as clinically tolerated. Significant effect occurs around 6 hours. Potential benefits of corticosteroids are shown in **Table 1**. Inhaled steroids are being investigated for asthma exacerbations. One such investigation suggested that several doses of inhaled corticosteroid had improved efficacy over IV therapy alone, but further confirmation is needed. Evidence indicates that inhaled corticosteroids can reduce the likelihood of relapse of exacerbation.

Table 1. Potential Benefits of Corticosteroids in Asthma

Enhancement of β_2-receptor responsiveness
Interruption of arachidonic acid inflammatory pathways
Decrease in capillary basement membrane permeability
Decrease in leukocyte attachment
Intracellular modulation of calcium migration
Reduction in airway mucus production
Suppression of immunoglobulin E receptor binding

Inhaled Anticholinergic Therapy

Ipratropium is an effective agent for obstructive airway disease and, when used with β-agonists, is more effective than either alone. The NIH expert panel recommends 0.5 mg of nebulized ipratropium every 30 minutes for 3 doses and then every 2 to 4 hours as needed. Ipratropium can be combined with the nebulized albuterol dose. The deposition of ipratropium can be enhanced, however, when it follows albuterol-induced bronchodilatation. In severe asthma, ipratropium can produce a clinically significant response within minutes of administration, as opposed to the longer delay to response in patients with COPD and chronic stable disease. If ipratropium is delivered by MDI (0.018 mg per puff), 4 to 8 puffs per treatment are recommended. If delivered by inhalation, ipratropium can be delivered combined with a β-agonist.

Theophylline

Theophylline is an effective bronchodilator compared with placebo in patients with acute bronchospasm, although inhaled β-agonists are superior. Theophylline

is most effective in controlling symptoms in patients with moderate asthma who also use inhaled corticosteroids. In the critical care setting, theophylline can be considered in those patients not responding to maximal standard therapy. A loading dose of 6 mg/kg over 30 minutes and an infusion rate of 0.5 mg/kg/h adjusted to achieve a level of 8 to 10 μg/L is recommended. The infusion rate is lower in patients with heart and liver dysfunction. The toxicity profile and narrow therapeutic index of this medication make it a high-risk–low-benefit choice for most patients, and it should be considered only after other measures have been exhausted.

Magnesium Sulfate

Magnesium reverses bronchoconstriction via inhibition of the calcium channel and decreased acetylcholine release. IV magnesium produces a small but clinically significant improvement in the most severe cases of acute asthma (FEV_1 <20%). Two grams of magnesium sulfate is administered IV over 20 minutes. Repeat doses may be used with caution in patients without renal disease and in whom levels and toxicity side effects are closely monitored.

Leukotriene Inhibitors

Leukotriene inhibitors have been accepted as maintenance therapy for patients with moderate or severe persistent asthma. The mechanism of action of these agents is inhibition of the cysteinyl leukotriene receptor, a pathway component linked to inflammatory mediators, bronchoconstriction, and smooth muscle edema. Randomized trials in asthma exacerbations have demonstrated that such agents can facilitate more rapid and complete resolution of airway obstruction when they are used in conjunction with standard therapy.

Alternative Agents

Considerable work is being done at cellular and genetic levels (“biologics”) to target the causes of asthma and to develop interventions that may ameliorate these factors. Examples include cytokine modifiers and suppression of interleukins 3, 4, 5, and 17, all of which have been implicated in asthma and asthma exacerbations. Although none of these medications are yet ready for prime time, they show considerable promise and will almost certainly be included in future editions of this chapter.

Mechanical Ventilation in Asthma

Indications

Mechanical ventilation should likely be undertaken if the patient has central cyanosis, altered sensorium, pH less than 7.25, respiratory distress with normal or elevated $PaCO_2$, or cardiopulmonary instability. Intubation should be accomplished using the technique in which the operator feels most proficient. The largest possible endotracheal tube should be selected to decrease the potential for and severity of auto–positive end-expiratory pressure (auto-PEEP).

Initiating Mechanical Ventilation

Initial ventilator settings depend on various factors, including the degree of ventilatory defect and ventilation-perfusion mismatch and the severity of air trapping. If volume ventilation is used, peak inspiratory flow rates should be set at 80 to 100 L/min with a square waveform to satisfy air hunger and minimize auto-PEEP. Air trapping (auto-PEEP) in severe asthma interferes with ventilation, oxygenation, and comfort and can increase barotrauma. Patients with air trapping seen on quantitative computed tomography scanning have increased risk for severe asthma exacerbations and hospital admission.

Mechanically ventilated asthmatic patients with severe air trapping often require heavy sedation, analgesia, and even paralytics. Assist-control ventilation without sedation and paralysis can cause hyperinflation if the patient's breathing rate is high. Sedation and/or paralysis will reduce carbon dioxide production, facilitate accurate pressure measurement, and facilitate effective ventilation.

Neuromuscular blockade, when combined with steroid therapy, increases the risk for ICU-acquired myopathy and should be discontinued as soon as possible. If the patient is to be continuously paralyzed, a peripheral nerve stimulator should be used to limit paralysis to a recording of 1 or 2 twitches in response to a train of 4 stimuli, as opposed to higher degrees of paralysis. Prolonged neuromuscular blockade may lead to persistent neuromuscular weakness following withdrawal of neuromuscular blockade. This situation is particularly likely to occur in patients with renal impairment, in females, in those with hypophosphatemia, and in patients receiving concomitant corticosteroids.

Aerosol Delivery

Aerosol delivery in the mechanically ventilated patient is challenging because reduced agent levels reach the lung parenchyma; much is deposited in the endotracheal tube, primarily because of its 90° curvature. Corrective strategies

include disconnecting the circuit as close to the patient as possible and using higher doses. An MDI with a spacer is less expensive than nebulized therapy and is generally considered to be as effective in delivering bronchodilator medication in mechanically ventilated patients.

Noninvasive Positive Pressure Ventilation

Increasing evidence shows that noninvasive positive pressure ventilation (NIPPV) can be useful in patients with severe asthma who do not have imminent ventilator failure. The use of NIPPV is generally contraindicated in patients with altered sensorium, abdominal disease, and advanced pregnancy. The effectiveness of NIPPV may be increased with the addition of a mild sedative, such as dexmedetomidine, targeted to minimize respiratory depression as a side effect.

Heliox

A mixture of helium and oxygen reduces turbulent flow in larger airways, facilitating expiratory flow, decreasing dynamic hyperinflation, and improving deposition of bronchodilators. Heliox is administered in concentrations of 80:20 or 60:40, with helium as the higher concentration agent. Despite encouraging observations, heliox is not yet considered standard of care because few randomized trials (particularly in adults) have been conducted to provide definitive evidence. Heliox can be used in the mechanically ventilated patient to decrease auto-PEEP, although randomized trials are lacking here as well. Its use in asthma should be reserved for those with hypercarbia or high airway pressures, where heliox has the greatest utility.

Nontraditional Asthma Therapy

Nontraditional treatment alternatives include intensification of β-agonist therapy and general anesthetic agents (ie, isoflurane, ketamine). Continuous IV albuterol has been used in Europe but is not available in the United States. It is unlikely to add any additional benefit over increasing the dose and frequency of administration of inhaled bronchodilators. IV isoproterenol and terbutaline have been used in children but are not recommended in adults.

COPD EXACERBATIONS AND ASSOCIATED ACUTE RESPIRATORY FAILURE

General Clinical Considerations

Oxygen should be administered to all patients with acute exacerbation of COPD, targeting arterial saturation values of 90% to 92% or PaO_2 of 60 to 65 mm Hg. Using the lowest FIO_2 that will accomplish this goal is important, because higher doses of oxygen can increase $PaCO_2$ levels by increasing dead space. Patients with COPD who have purulent sputum in the absence of radiographically confirmed pneumonia should be treated with antibiotics, especially those with severe exacerbations. Most studies recommend a corticosteroid course of 10 to 14 days. Unloading fatigued muscles using NIPPV can improve ventilation.

Diaphragm Function

During a COPD exacerbation, the increase in airway flow limitation often results in air trapping, increased work of breathing, reduction in both chest wall and lung compliance, and development of auto-PEEP that requires the patient to generate increased negative pleural pressure to initiate inspiratory flow. As the muscles of inspiration lengthen in response to severe air trapping, the optimal length-tension relationship is exceeded. Use of accessory inspiratory muscles can be seen with increasing severity of COPD exacerbation. With inspiration, the diaphragm normally moves down as it contracts, forcing the abdominal contents out. With diaphragmatic fatigue, the diaphragm no longer functions as a primary muscle of inspiration but instead assists the intercostal muscles' inspiratory effort by fixing the rib cage. This action is associated with a rise in the diaphragm, and the abdomen moves in. This is called *paradoxical breathing*. This sign implies respiratory muscle fatigue and often imminent ventilatory failure.

A recent Italian study examining which mechanical determinants of ventilatory failure have the greatest impact revealed that reduced muscular pressure generation and increased respiratory load were the most predominant factors. The respiratory control center was not believed to be a major factor in respiratory failure.

Medical Therapy

Treatment of an exacerbation of COPD warranting ICU admission is similar to treatment of severe asthma, with the following exceptions: Reversibility of obstructive airway disease is never complete, it is less likely to be dramatically improved with aggressive bronchodilator therapy, β-agonist toxicity is more likely, and no role has been established for magnesium or leukotriene inhibitors.

Patients with COPD are likely to be older than asthma patients and to have greater risk for coronary artery disease and malignant arrhythmias. Given this, the use of theophylline and epinephrine is discouraged. Combined β-adrenergic agonist and ipratropium are indicated, as in asthma. Also as in asthma, equivalent bronchodilation can be achieved with MDIs or nebulizers. Steroids are effective in ameliorating bronchoconstriction, smooth muscle edema, and airway mediators of inflammation in hospitalized patients with COPD.

A randomized double-blinded trial compared 2 weeks of systemic corticosteroids, 8 weeks of systemic corticosteroids, and placebo in hospitalized patients with COPD exacerbations. Both steroid treatment groups demonstrated improved outcome compared with placebo (shortened hospital stay, higher FEV_1 through 6 months). No difference was found between 2 weeks and 8 weeks of steroid therapy (the regimens were the same for the first 2 weeks). Hyperglycemia was more common in the steroid groups. The 2-week therapy consisted of IV methylprednisolone 125 mg every 6 hours for 72 hours and then a sequence of oral prednisone: 60 mg for 4 days, 40 mg for 4 days, and 20 mg for 4 days. A recent similar study demonstrated that higher dose steroids in the first 48 hours of a COPD exacerbation (defined as >240 mg/d methylprednisolone or equivalent) conferred no benefit over lower dose steroids and was associated with an increased risk of complications and side effects. Precipitating factors for exacerbation of COPD are listed in **Table 2**.

Table 2. Precipitating Factors for Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease

Pneumonia
Congestive heart failure
Infectious bronchitis
Pulmonary embolism
Medications, benzodiazepines, β-blockers (includes topical ophthalmic medications)
Worsening of reversible airway obstruction

Mechanical Ventilation of COPD

Auto-PEEP poses a similar problem in COPD as in asthma, although achieving

adequate alveolar ventilation is often less challenging in COPD. Peak inspiratory airway pressures are usually lower because of less intense airway edema and mucous plugging as well as an increase in compliance attributable to baseline pathophysiological disease status in COPD (emphysema). Emphysema decreases elastic recoil that would increase risk of auto-PEEP. Regional hyperinflation can occur, with high peak pressures due to heterogeneity of filling. Patients may present with “chronic” or “acute on chronic” respiratory acidosis, and the decision to intubate from the standpoint of arterial blood gas should be based on pH, not $Pa{CO_2}$.When chronic respiratory acidosis is present, caution should be exercised, because mechanical ventilation to a normal $Pa{CO_2}$ can produce severe alkalemia as well as renal “dumping” of bicarbonate, such that weaning the patient at a later time can be difficult.

Heliox

Three studies suggest potential utility of heliox in decompensated COPD. One study compared 70:30 nitrogen-oxygen with 70:30 helium-oxygen in mechanically ventilated patients with severe COPD. The patients receiving the helium mixture had a mean decrease in trapped gas volume of 215 mL and a mean decrease in auto-PEEP of 9 cm H_2O. A potential limitation of this technique is hypoxemia if patients require $F{IO_2}$ greater than 0.30. Two studies have examined the potential benefit of helium-oxygen mixtures delivered with NIPPV in acute exacerbations of COPD. One small study showed a reduced respiratory muscle pressure–time index (as a measure of effort to breathe) when helium-oxygen was compared with air-oxygen at both low and high NIPPV pressure support ventilation (PSV) levels. A second study showed that NIPPV with helium–oxygen, compared with NIPPV with air–oxygen, produced a greater decrease in inspiratory-expiratory (I:E) ratio as well as $Pa{CO_2}$.

Use of NIPPV in COPD-Induced Acute Respiratory Failure

NIPPV has proven efficacious in acute respiratory failure due to COPD in several clinical studies, with success rates as high as 65%. Several studies of NIPPV in COPD demonstrated decreased need for endotracheal intubation, length of stay, and mortality. A recent case-control study concluded that the use of 2 hours of NIPPV was associated with lower risk of nosocomial infections, less antibiotic use, shorter length of ICU stay, and lower mortality rates than in cohorts in whom NIPPV was not used. A meta-analysis published in 2015 studied more than 7,365 patient and demonstrated improved survival in those in

whom NIPPV was used instead of conventional mechanical ventilation. Among those studied were patients with COPD, pulmonary edema, and respiratory failure of mixed origins.

Physiological Effects

NIPPV decreases work of breathing, improves alveolar ventilation while resting the respiratory musculature, and improves gas exchange due to an increase in alveolar ventilation without observable change in ventilation-perfusion matching. Transdiaphragmatic pressure, diaphragmatic pressure-time product, and diaphragmatic electromyography amplitude are all decreased with NIPPV.

Potential physiological benefits of NIPPV in COPD include increased tidal volume, improved gas exchange, decreased respiratory rate and heart rate, improvement in oxygenation, and decreased diaphragm strain. A reduction in arterial carbon dioxide with a concomitant improvement in pH is also likely. When these beneficial responses occur, they are typically seen in the first several hours after initiation of NIPPV.

Ventilator-Patient Interface

NIPPV can be accomplished using a face or nasal mask connected through standard ventilator tubing to a traditional mechanical ventilator or a ventilator made specifically to deliver NIPPV. The nasal mask is less effective in mouth breathers and edentulous patients but also creates less dead space, causes less claustrophobia, minimizes potential complications in case of vomiting, and allows both expectoration and oral intake of fluid. Patients are coached to keep the mouth shut and use chin straps to reduce mouth leak. Face masks are preferable in severely dyspneic patients, because the nasal resistance to breathing is decreased with combined nose and mouth air entry. One recent study demonstrated that the nasal mask was better tolerated but the face mask gave higher minute ventilation and lower $Paco_2$. NIPPV is not recommended for patients with swallowing dysfunction or difficulty clearing secretions.

Indications

According to the consensus statement of the American Association for Respiratory Care, initiation of noninvasive ventilation in patients with COPD is recommended when 2 or more of the following criteria are present:

- Respiratory distress with moderate-severe dyspnea

- pH less than 7.35 with Pa_{CO_2} greater than 45 mm Hg
- Respiratory rate of more than 24 breaths per minute

Ventilator Selection for NIPPV

Several types of ventilators specifically designed for NIPPV, with both pressure-limited and volume-cycled modes, are available. Advantages of specific ventilators made for NIPPV include smaller size, portability, and less expense. Standard microprocessor-controlled ventilators used for invasive ventilation also can be used. These ventilators offer a number of advantages over portable units made for NIPPV:

- Precisely measured and high concentrations of oxygen can be delivered.
- Separate inspiratory and expiratory tubing minimizes carbon dioxide rebreathing.
- Large mask leaks or patient disconnection can be more readily detected.
- Monitoring and alarm features are more sophisticated.

Several choices of ventilatory mode are available that include assist control (either volume ventilation or pressure control ventilation) and PSV. PSV is likely better tolerated than assist-control mask ventilation and provides greater patient-ventilator synchrony, but no studies are available that demonstrate outcome benefit.

Air leaks are a common problem associated with the use of NIPPV, particularly given the variability in masks and ventilator performance. A recent trial compared 9 ventilators (via simulators) with respect to tidal volumes, airway pressures, and synchrony. Only 2 ventilators (the Servo I [Maquet, Rastatt, Germany] and the Vision [Respironics, San Francisco, CA]) required no adjustment with increasing air leaks. This finding may have major implications when one is choosing ventilators for patients with respiratory failure and the need for reliability and synchrony.

Initial Approach and Maintenance of NIPPV

Explaining the procedure in detail to the patient facilitates cooperation, acceptance, and success. The face mask is recommended for initial use in most patients. Close surveillance and monitoring by healthcare personnel, ideally in a

step-down or ICU bed, are advised. The patient should take nothing by mouth during initial ventilation until success of NIPPV is clear.

For PSV, the initial inspiratory support pressure is set between 5 and 15 cm H_2O above an end-expiratory pressure (EEP, synonymous with PEEP) setting and increased slowly over time, as tolerated, to achieve target Pa_{CO_2} level. With the assist-control and volume-cycled mode, the starting tidal volume is 8 mL/kg of ideal body weight and is adjusted up or down for tolerance and effect on Pa_{CO_2} level. PSV is set at 5 to 8 cm H_2O above EEP and then titrated up to the desired tidal volume. Evidence supports an efficient breathing pattern as the primary goal during NIPPV. Tidal volume is gradually increased according to patient tolerance, targeting a pH of 7.32 to 7.35. With ventilators made for NIPPV, the EEP is typically set at 4 to 5 cm H_2O to facilitate function of ventilator. With standard ventilators, this is not necessary. Patients who respond to NIPPV typically have rapid synchronization with the ventilator and a decrease in respiratory rate, heart rate, and Pa_{CO_2} during the first several hours of ventilation. In the absence of these improvements over the first several hours, intubation and invasive mechanical ventilation are advisable.

Although NIPPV has been used for a variety of causes of acute respiratory failure, success is more likely in hypercapnic respiratory failure due to COPD (**Table 3**). In this circumstance, NIPPV is a temporizing measure until bronchodilator and anti-inflammatory therapy leads to improvement. Early fiberoptic bronchoscopy in combination with NIPPV should be considered for COPD patients because this combination has shown promise in reducing the need for mechanical ventilation. The purported mechanism by which this is useful entails control of secretions related to the underlying obstruction.

Table 3. Noninvasive Positive Pressure Ventilation in Chronic Obstructive Pulmonary Disease

The COPD patient with acute on chronic respiratory acidosis is probably best suited for this technique.
Patients can receive NIPPV through either full-face mask or nasal mask using mechanical ventilators developed specifically to deliver NIPPV, or NIPPV can be administered with traditional mechanical ventilators. The former are perhaps more easily used and more portable, although there are no studies to demonstrate better outcome using either type of machine support.
NIPPV is most likely to be effective in a fully oriented, cooperative patient in whom a good seal can be obtained. Edentulous patients pose significant problems when the nasal mask is used.

A patient considered for NIPPV should ideally have single organ failure (ie, no hemodynamic instability, no acute upper gastrointestinal hemorrhage, no myocardial ischemia or infarction).
Initial settings are typically 5 cm H_2O EPAP and 12 cm H_2O IPAP.
IPAP should be titrated up for a greater inspiratory boost, leaving the EPAP at the initial setting of 5 cm H_2O; IPAP is titrated to obtain acceptable pH.
Although various pressure or volume modes of ventilation can be used, the pressure support mode is probably best tolerated in the alert and oriented patient.

Abbreviations: COPD, chronic obstructive pulmonary disease; EPAP, expiratory positive airway pressure; IPAP, inspiratory peak airway pressure; NIPPV, noninvasive positive pressure ventilation.

General recommendations for the use of NIPPV in COPD are as follows:

- For pressure-cycled ventilation, it is best to start at lower inspiratory pressures and gradually increase to target level.
- Gastric distension is unlikely to occur with peak inspiratory pressure less than 25 cm H_2O.
- NIPPV should not be used in rapidly deteriorating patients who are at risk of sudden respiratory arrest.
- NIPPV should not be used unless the physician or the respiratory therapist is familiar with the technical operation and fitting of the device.
- Use of NIPPV should be considered primarily in alert, oriented, hemodynamically stable, and cooperative patients with hypercapnic respiratory failure, and especially hypercapnic respiratory failure due to COPD.
- Initially, a pressure-support mode with 5 to 12 cm H_2O applied inspiratory pressure above expiratory positive airway pressure (EPAP) or PEEP should be used. The potential positive-pressure boost to inspiration is directly correlated with the difference between inspiratory pressure and end-expiratory pressure levels. For hypercapnic respiratory failure, a low EPAP (PEEP) setting is chosen. Some NIPPV ventilators require a low EPAP setting to function properly.
- When ventilators that are made specifically for NIPPV are used, additional

supplemental oxygen may be bled directly into the pressure tubing at the mask and titrated to maintain adequate oxygenation.

- The patient's vital signs, clinical appearance, and arterial blood gases should be monitored. Inability to improve patient status within several hours makes success unlikely.
- Oral intake should be restricted until effectiveness in reversing acute ventilatory failure is ensured.
- Patients receiving NIPPV must be monitored as closely as any other patient with acute respiratory deterioration and should be placed in an ICU or respiratory care unit. Continuous pulse oximetry and cardiac monitoring are desirable.

Weaning From NIPPV

Weaning from NIPPV can be accomplished either by progressively decreasing the levels of inspiratory positive pressure support or by permitting the patient to be intermittently off NIPPV for increasing lengths of time. A combination of both strategies can be used. In general, it is useful to wean patients by progressively lengthening the period of spontaneous breathing without NIPPV. Once the crisis is over, many patients can be weaned relatively quickly. Unlike invasive ventilation, NIPPV can be reinstituted easily and quickly if the patient shows signs of fatigue or intolerance to spontaneous breathing. Nocturnal NIPPV may be needed during the early weaning period and can be continued at home in some patients. At least 2 studies have demonstrated advantage of NIPPV over traditional weaning, and in another study NIPPV was used successfully to avoid reintubation of postextubation hypercarbia patients. The use of NIPPV in acute respiratory failure has been confirmed to have a positive impact on survival and the reduction of ventilator-associated pneumonia.

Dynamic Hyperinflation and Auto-PEEP (Intrinsic PEEP)

Auto-PEEP occurs when ventilator settings dictate an I:E ratio that does not allow adequate expiratory time. After the first breath is delivered in a setting conducive to auto-PEEP, the next breath is delivered prior to complete emptying of the previous breath. Thereafter, with each subsequent breath that fails to completely empty, end-expiratory lung volume increases, as do flow and pressure at end-expiration. This causes significant elevations in end-expiratory pressure not set on the ventilator (auto-PEEP), mean airway pressure, and

intrathoracic pressure. This process can be accompanied by a marked elevation in intrathoracic pressure and associated hypotension (decreased venous return to heart) and barotrauma (pneumothorax).

Auto-PEEP can be detected easily with graphic flow displays showing expiratory gas flow still present at the onset of the next inspiration. When no other obvious cause is present (eg, tension pneumothorax), auto-PEEP should be suspected in patients who are hypotensive after institution of mechanical ventilation, especially in the presence of obstructive airway disease. Higher minute ventilation, particularly in assist-control ventilation in the awake patient in distress, predisposes the patient to auto-PEEP. Auto-PEEP is treated by decreasing the total inspiratory time. This requires heavy sedation in most cases and neuromuscular blocking agents in some. Decreasing tidal volume also is effective but is less efficient. If hypotension ensues, increasing expiratory time is a diagnostic and therapeutic maneuver. Unless inspiratory flow rate was set inappropriately low (<80 L/min), shortening the total inspiratory time by increasing flow rate is a less effective way of decreasing auto-PEEP. The I:E ratio is not a good barometer of risk for auto-PEEP. Increasing the actual time for expiration made available for each breath correlates best with successful treatment of auto-PEEP.

Extracorporeal Carbon Dioxide Removal in Obstructive Lung Diseases

The presence of extracorporeal gas exchange therapies is becoming increasingly common through the United States and the world. Most commonly, this therapy takes the form of extracorporeal membrane oxygenation (ECMO) and is directed at those patients with reversible severe oxygenation disorders or those who are bridging to lung transplant. More recently, however, investigators have begun studying the utility of extracorporeal carbon dioxide removal (ECCO) in those patients who are retaining large amounts of carbon dioxide and who have commensurate refractory acidosis. Such patients are very often those with obstructive lung diseases like COPD and asthma. In a 2015 study, investigators compared patients with severe COPD exacerbations on NIPPV with and without the use of ECCO. The former group was 3 times less likely to require invasive mechanical ventilation than the group in which ECCO was not used.

Similar case reports in patients with severe exacerbations of asthma are emerging and show legitimately promising potential. Not surprisingly, there are fewer patients with asthma who might be considered for this therapy since they

tend not to retain carbon dioxide to the same degree as their COPD equivalents.

Vaccine Recommendations for Patients With Asthma and COPD

Patients with asthma and COPD are known to be at increased risk for bacterial and viral infections. Many such infections prove to be fatal when combined with the underlying disease. It is imperative that providers be well versed with current vaccine recommendations for these groups and that this issue be addressed at each outpatient visit and with each inpatient admission (**Table 4**).

Table 4. Vaccine Recommendations in Asthma and Chronic Obstructive Pulmonary Disease

Vaccine	Frequency
Influenza	Annually
Pneumococcus	Every 5 y until after age 65 y
Pertussis (TdaP)	Once
Herpes zoster	Once, age >65 y

Information taken from Centers for Disease Control and Prevention. *Centers for Disease Control and Prevention 2016.* Available at: http//www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm.

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CHAPTER 21

Principles of Mechanical Ventilation

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Key words: respiratory system mechanics, pressure-targeted breaths, flow-targeted breaths, intrinsic positive end-expiratory pressure, complications of mechanical ventilation

Mechanical ventilation is the process of using positive pressure devices to either totally or partially provide oxygen and carbon dioxide transport between the environment and the pulmonary capillary bed. The desired effect of mechanical ventilation is to maintain adequate levels of P_{O_2} and P_{CO_2} in arterial blood while unloading the inspiratory muscles. This process should be done in a manner that avoids injury to the lungs and other organ systems.

Over the last 2 decades, a sizeable evidence base has emerged to guide clinicians in providing safe and effective support with conventional strategies. At the same time, an array of clever innovations have been introduced, many of which await more definitive outcome studies before they can be considered standard of care. This chapter reviews the design principles underlying these devices, the physiological consequences of positive pressure ventilation, current thoughts on applying safe and effective support delivery, and some promising emerging technologies.

DESIGN FEATURES OF POSITIVE PRESSURE MECHANICAL VENTILATION

Most modern ventilators use piston-bellows systems or controllers of high pressure sources to drive gas flow. Tidal breaths are generated by this gas flow and can be either controlled entirely by the ventilator or interactive with patient efforts. Generally, pneumatic, electronic, or microprocessor systems provide for various breath types to be available. These can be classified by what initiates the

breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).

Trigger variables are either patient effort (detected by the ventilator as a pressure or flow change) or a set machine timer. Target or limit variables are generally either a set flow or a set inspiratory pressure. Cycle variables are generally a set volume, a set inspiratory time, or a set flow. High pressure is usually also present as a backup safety cycle variable. Together, these 3 variables can describe the 5 basic breaths available on most modern mechanical ventilators: the volume control breath (timer triggered, flow targeted, volume cycled), the volume assist breath (effort triggered, flow targeted, volume cycled), the pressure control breath (timer triggered, pressure targeted, time cycled), the pressure assist breath (effort triggered, pressure targeted, time cycled), and the pressure support breath (effort triggered, pressure targeted, flow cycled) (**Table 1**). The availability and delivery logic of different breath types define the 5 common modes of mechanical ventilatory support (**Table 2**). The mode controller is an electronic, pneumatic, or microprocessor-based system that is designed to provide the proper combination of breaths according to set algorithms and feedback data.

Table 1. The 5 Basic Breaths Available on Most Modern Mechanical Ventilators Classified According to Trigger, Target/Limit, and Cycle Criteria

Breath Type	**Trigger**	**Target/Limit**	**Cycle**
Volume control (VC)	Timer	Flow	Volume
Volume assist (VA)	Effort	Flow	Volume
Pressure control (PC)	Timer	Pressure	Time
Pressure assist (PA)	Effort	Pressure	Time
Pressure support (PS)	Effort	Pressure	Flow

Table 2. Breath Types Available on Common Modes of Mechanical Ventilation

Breath Types

Mode	VC	VA	PC	PA	PS	Sp
Volume assist control	X	X				
Pressure assist control			X	X		
Volume SIMV	X	X			X	X

Pressure SIMV			X	X	X	X
Pressure support					X	

Abbreviations: PA, pressure assist; PC, pressure control; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation; Sp, spontaneous unassisted; VA, volume assist; VC, volume control.

In recent years, feedback systems have been developed for these basic modes and are now available on many modern devices. These include pressure-regulated volume control, volume support, and adaptive support ventilation. Pressure-regulated volume control and volume support are pressure-targeted modes (time cycled and flow cycled, respectively) in which the ventilator automatically adjusts the inspiratory pressure to maintain a target volume. Adaptive support ventilation is also a pressure-targeted mode with an inspiratory pressure feedback algorithm, but the inputs with adaptive support ventilation include a work of breathing calculation (the goal is to minimize applied work) and respiratory timing patterns. Pressure-regulated volume control, volume support, and adaptive support ventilation have all been shown in clinical studies to perform as designed, but none have been shown in randomized trials to provide better outcomes than more conventional standard of care approaches.

Two new modes of support have been introduced over the last decade: proportional assist ventilation and neutrally adjusted ventilator assistance. Proportional assist ventilation calculates patient mechanical properties through controlled test breaths. It then monitors patient effort and delivers additional pressure, flow, and volume to offset a clinician-selected percentage of the patient's work of breathing. Neutrally adjusted ventilator assistance uses an esophageal catheter that has an array of electromyographic electrodes. These are placed at the level of the diaphragm, and the electromyographic signal is used to trigger breaths, adjust delivered flow, and cycle ventilator breaths. In theory, both proportional assist ventilation and neutrally adjusted ventilator assistance should enhance patient-ventilator synchrony, and in small trials these modes have been shown to behave as designed. However, randomized trials have not been conducted that show superior outcomes with these modes compared with conventional standard of care approaches.

PHYSIOLOGICAL EFFECTS OF POSITIVE PRESSURE MECHANICAL VENTILATION

Respiratory System Mechanics

Equation of Motion

Lung inflation during mechanical ventilation occurs when pressure and flow are applied at the airway opening. These applied forces interact with respiratory system compliance (both lung and chest wall components), airway resistance, and, to a lesser extent, respiratory system inertance and lung tissue resistance to effect gas flow. For simplicity, because inertance and tissue resistance are relatively small, they can be ignored such that the interactions of pressure, flow, and volume with respiratory system mechanics can be expressed by the simplified equation of motion:

Circuit Pressure + Muscle Pressure = (Flow × Resistance) + (Volume / System Compliance).

In the mechanically ventilated patient, this relationship is expressed as

$$P_{cir} + P_{mus} = (V' \times R) + (V_T / C_{rs}) + PEEP,$$

where P_{cir} is the ventilator circuit pressure; P_{mus} is inspiratory muscle pressure generated by patient effort; V' is the flow into the patient's lungs; R is the resistance of the circuit, artificial airway, and natural airways; V_T is the tidal volume; C_{rs} is the respiratory system compliance; and PEEP is positive end-expiratory pressure.

During a passive breath ($P_{mus} = 0$), performing an inspiratory hold at end inspiration (ie, no-flow conditions: $V' = 0$), the P_{cir} "plateaus" and is commonly referred to as the plateau pressure (P_{plat}). The components of P_{cir} required for flow and for respiratory system distension can be separated using this inspiratory hold. Specifically, calculating the difference in P_{cir} during flow and during no-flow (the "peak to plateau difference") allows for a calculation of inspiratory airway resistance ($R = P_{peak} – P_{plat} / V'$); P_{plat} – PEEP reflects the driving pressure (DP), which allows for the calculation of C_{rs} ($C_{rs} = V_T / DP$).

Separating the 2 components of C_{rs}—chest wall compliance (C_{cw}) and lung compliance (C_l)—can be done during a passive positive pressure breath using a measurement of esophageal pressure (P_{es}) to approximate pleural pressure. With this measurement, the inspiratory change in P_{es} (ΔP_{es}) can be used in the

following calculations: $C_{cw} = V_T / \Delta P_{es}$ and $C_l = V_T / (DP - \Delta P_{es})$.

Lung distention during inspiration and expiration is dependent on the transpulmonary pressure (TPP), the pressure inside the alveolus minus the pressure outside the alveolus or pleural space. At end inspiration, this is the P_{plat} minus the P_{es}. In clinical practice, because C_{cw} usually is quite high and P_{es} is thus quite low, P_{plat} is often taken as an approximation of lung distending pressure alone. However, in situations where C_{cw} is reduced (eg, obesity, anasarca, ascites, and surgical dressings), the stiff chest wall will raise P_{es} and will cause P_{plat} to overestimate TPP. Conversely, if patient efforts are present during inspiration, these generated negative P_{es} values will cause measured P_{cir} to underestimate TPP.

Pressure-Targeted Versu Flow-Targeted Breaths

The 2 basic approaches to delivering positive pressure breaths are flow targeting and pressure targeting. Changes in compliance, resistance, or patient effort will change P_{cir} (but not flow) with a flow-targeted breath. In contrast, similar changes in compliance, resistance, or effort will cause a change of V_T (but not P_{cir}) with the pressure-targeted breath. From a clinical perspective, both breath types can be set to deliver similar V_T and inspiratory times. However, the design features of the flow-targeted (and volume-cycled) breath can be useful in patients who need a guaranteed V_T, whereas the design features of the pressure-targeted (and either time-cycled or flow-cycled) breaths can be useful in patients with vigorous spontaneous flow demands. As noted, the feedback features of pressure-regulated volume control, volume support, and adaptive support ventilation conceptually provide a hybrid of these 2 breath types.

Intrinsic PEEP

Intrinsic PEEP is PEEP that develops within the alveoli when either inadequate expiratory time or collapsed airways during expiration (or both) prevent the lung from reaching its normal resting volume. Intrinsic PEEP depends on 3 factors: minute ventilation, the expiratory time fraction, and the respiratory system expiratory time constant (the product of resistance and compliance). As minute ventilation increases, the expiratory time fraction decreases, and the time constant lengthens (ie, higher R or C_{rs} values), the potential for intrinsic PEEP to develop increases.

The development of intrinsic PEEP will have different effects on pressure-targeted versus flow-targeted ventilation. In flow-targeted ventilation, the constant delivered flow and volume (and thus DP) in the setting of an increasing intrinsic PEEP will increase both the P_{peak} and the P_{plat}. In contrast, in pressure-targeted ventilation, the set P_{cir} limit coupled with an increasing intrinsic PEEP level will decrease DP and thus the delivered V_T (and minute ventilation). This can help limit the buildup of intrinsic PEEP in pressure-targeted modes.

In the passive patient, intrinsic PEEP can be assessed in 2 ways. First, when an inadequate expiratory time is producing intrinsic PEEP, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, intrinsic PEEP in alveolar units that have patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the intrinsic PEEP with P_{cir}.

In patients with active respiratory drives, the expiratory hold maneuver is impossible to perform. However, intrinsic PEEP can be assumed to be present again if the expiratory flow has not reached zero before breath initiation occurs. As noted in more detail later, intrinsic PEEP can function as an important inspiratory threshold load on patient effort. This is best quantified by using an esophageal balloon to estimate pleural pressures. With this technique, the effort-related change in P_{es} before P_{cir} change is a reflection of the threshold load imposed by intrinsic PEEP.

Distribution of Ventilation

A positive pressure tidal breath must distribute among the millions of alveolar units in the lung. Factors affecting this distribution include regional resistances, compliances, functional residual capacities, and the delivered flow pattern (including inspiratory pause). In general, positive pressure breaths will tend to distribute more to units with high compliance and low resistance and away from obstructed or stiff units. This creates the potential for regional overdistension of healthier lung units, even in the face of V_T that is considered normal.

Alveolar Recruitment and Gas Exchange

Parenchymal lung injury produces ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching and shunts because of alveolar inflammation, flooding, and collapse. In many of these disease processes, substantial numbers of collapsed alveoli can be recruited during a positive pressure ventilatory cycle. Additional recruitment can be

provided sometimes with the use of formal recruitment maneuvers or prolongation of inspiratory time. The application of PEEP is designed to prevent derecruitment during exhalation.

Inspiratory Time Prolongation

Inspiration from a positive pressure breath consists of a flow magnitude and a flow profile that can affect ventilation distribution (and thus $\dot{V}/\dot{Q}$ matching). Prolonging inspiratory time, generally by adding a pause and often used in conjunction with a rapid decelerating flow (ie, pressure-targeted breath), has several physiological effects. First, the longer inflation period may recruit more slowly recruitable alveoli. Second, increased gas mixing time may improve $\dot{V}/\dot{Q}$ matching in parenchymal lung injury (pendelluft). Third, the development of intrinsic PEEP from consequently shorter expiratory times can have effects similar to those of applied PEEP. However, the distribution of intrinsic PEEP (most pronounced in lung units with long time constants) can be different from that of applied PEEP, and thus $\dot{V}/\dot{Q}$ effects can also be different. Fourth, because these long inspiratory times significantly increase total intrathoracic pressures, cardiac output can be affected (see below). Fifth, inspiratory-expiratory (I:E) ratios that exceed 1:1 (so-called inverse ratio ventilation) are uncomfortable, and patient sedation or paralysis is often required unless a relief mechanism allows spontaneous breathing during the inflation period (ie, airway pressure release ventilation, or APRV).

Positive End-Expiratory Pressure

PEEP is defined as an elevation of P_{alv} at the end of expiration. As noted previously, PEEP can be produced either by expiratory circuit valves (applied PEEP) or as a consequence of ventilator settings interacting with respiratory system mechanics and producing long expiratory time constants (intrinsic PEEP). Expiratory muscle contraction can also raise intrathoracic pressures at end expiration, but this does not increase TPP.

Importantly, C_{cw} can have profound effects on alveolar recruitment throughout the ventilatory cycle. Indeed, if C_{cw} is markedly reduced and P_{es} exceeds set circuit PEEP at end expiration, the TPP will be a negative value reflecting alveolar collapse.

The ability of PEEP to prevent alveoli from being derecruited provides several potential benefits. First, recruited alveoli improve $\dot{V}/\dot{Q}$ matching and gas

exchange throughout the ventilatory cycle. Second, as discussed in more detail subsequently, patent alveoli throughout the ventilatory cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing. Third, PEEP prevents surfactant breakdown in collapsing alveoli and thus improves C_l. This is the rationale behind applying PEEP after a recruitment maneuver: Recruited alveoli are on the deflation limb of the pressure-volume relationship, and thus the PEEP required to maintain recruitment is lower than that required for initial recruitment.

PEEP can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually increased by PEEP application (although this increase may be less than the actual increased PEEP level because of PEEP-induced improved compliance). This increase must be considered if the lung is at risk for regional overdistension (discussed later). Moreover, since parenchymal lung injury is often quite heterogeneous, PEEP that is appropriate in one region can be suboptimal in another and yet excessive in another. Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure. This can compromise cardiac filling in susceptible patients (discussed subsequently).

PATIENT-VENTILATOR INTERACTIONS

Mechanical ventilation modes that permit spontaneous ventilatory activity are termed *interactive modes* in that patients can affect various aspects of the mechanical ventilator's functions. These interactions can range from simple triggering of mechanical breaths to more complex processes affecting delivered flow patterns and breath timing. Interactive modes allow for muscle "exercise," which, when done at nonfatiguing or physiological levels, can prevent atrophy (ventilator-induced diaphragmatic dysfunction) and facilitate recovery from fatigue. Permitting spontaneous patient ventilatory activity and using comfortable interactive modes can reduce the need for the sedatives and neuromuscular blockers that are often required to prevent patients from "fighting" machine-controlled ventilation.

Interactive modes can be either synchronous or dyssynchronous with patient efforts. With synchronous interactions, the ventilator is sensitive to the initiation, modulation, and termination of a patient's ventilatory effort. Dyssynchronous

interactions lead to patient discomfort, unnecessary sedation, prolonged duration of mechanical ventilation, and even increased morbidity and mortality.

Synchrony is best assessed by clinical observations and analysis of airway pressure graphic over time. Clinical signs of dyssynchrony are tachypnea, dyspnea, diaphoresis, and tachycardia, and the patient is often described as "fighting" the ventilator. Graphically, trigger dyssynchrony is manifest by excessive negative airway pressure signals preceding breath triggering (insensitive trigger systems) or the absence of any flow delivery in response to observed effort (threshold load from intrinsic PEEP). Flow dyssynchrony is a consequence of inadequate flow delivery and is manifest by the airway pressure graphic during flow delivery being pulled (or "sucked") downward during inspiration. Cycle dyssynchrony is manifest by continued patient effort and sometimes double triggering if the cycle is too early. Cycle dyssynchrony can also be manifest as increases in airway pressure from expiratory muscle activity if the cycle is too long.

POSITIVE PRESSURE VENTILATION AND CARDIAC FUNCTION

In addition to affecting ventilation and ventilation distribution, intrathoracic pressure applications from positive pressure ventilation can affect cardiovascular function. In general, as mean intrathoracic pressure is increased, right ventricular filling is decreased, right ventricular afterload is increased, and cardiac output and pulmonary perfusion consequently decrease. Indeed, the reduced venous return is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. Of note, however, is that positive pressure ventilation can also improve left ventricular function when elevated intrathoracic pressures reduce left ventricular afterload. Thus, in patients with left-sided heart failure, the reduced cardiac filling and reduced left ventricular afterload effects of elevated intrathoracic pressure can actually improve cardiac function. Under these conditions, removal of intrathoracic pressure can produce weaning failure. An interesting corollary to these concepts is the notion of using high-frequency ventilation (HFV) timed to ventricular systole to augment cardiac output in patients with severe heart failure.

Intrathoracic pressures can influence distribution of perfusion. The relationship of alveolar pressures to perfusion pressures in the West 3-zone lung model helps explain this. Specifically, the supine human lung is generally in a zone 3 (distension) state. As intra-alveolar pressures increase, however, zone 2 and zone 1 (dead space) regions can appear, creating high $\dot{V}/\dot{Q}$ units. Indeed, increases in

dead space can be a consequence of ventilatory strategies using high ventilatory pressures as well as with settings producing intrinsic PEEP buildup.

Positive pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catechol release with subsequent increases in myocardial oxygen demands and risk of dysrhythmias. Oxygen delivery by coronary blood vessels can be compromised by inadequate gas exchange from the lung injury coupled with low mixed venous PO_2 attributable to high oxygen consumption demands by the inspiratory muscles.

COMPLICATIONS OF MECHANICAL VENTILATION

Ventilator-Induced Lung Injury

The lung can be injured when it is stretched excessively by positive pressure ventilation. The most well-recognized injury is alveolar rupture presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleura (pneumothorax), and vasculature (air emboli). The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistension. Thus, interactions of respiratory system mechanics and mechanical ventilation strategies (high regional V_T and PEEP, both applied and intrinsic) that produce regions of excessive alveolar stretch (ie, transpulmonary distending pressures >40 cm H_2O) for prolonged periods create alveolar units at risk for rupture.

Parenchymal lung injury not associated with extra-alveolar air (ventilator-induced lung injury, or VILI) can be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum (ie, transpulmonary distending pressures of 30 cm H_2O). This is termed *excessive lung stress* in engineering parlance. Importantly, VILI is likely more than simply a consequence of excessive end-inspiratory stretch or lung stress. Excessive tidal stretch (ie, repetitive cycling of the lung with higher than normal V_T), even in the setting of acceptable lung stress (ie, P_{plat} <30 cm H_2O), can contribute to VILI. In engineering terms, tidal stretch, when referenced to the end-expiratory volume, is called *lung strain*. Importantly, in heterogeneously injured lungs (typical of most disease states), the excessive stress and strain occur predominantly in the more compliant and better aerated (ie, more “normal”) lung regions. Regional protection of these healthier lung units is the rationale for

using lung-protective ventilator strategies that accept less than normal values for pH and P_{O_2} in exchange for lower (and safer) distending pressures (discussed subsequently).

Other ventilatory pattern factors can be involved in the development of VILI. These include frequency of stretch and the acceleration and velocity of stretch. Although VILI may not be affected by fixed atelectasis, it does appear to be potentiated by a shear stress phenomenon that occurs when injured alveoli are repetitively opened and collapsed during the ventilatory cycle (ie, cyclical atelectasis). Vascular pressure elevations can also contribute to VILI.

VILI is manifest pathologically as diffuse alveolar damage. Moreover, VILI is associated with cytokine release and bacterial translocation that are implicated in the systemic inflammatory response with multiple-organ dysfunction that results in VILI-associated mortality.

Oxygen Toxicity

Oxygen concentrations approaching 100% are known to cause oxidant injuries in airways and lung parenchyma. Much of the data supporting this concept, however, have come from animals that often have quite different tolerances to oxygen than humans. It is thus not clear what the "safe" oxygen concentration or duration of exposure is in sick humans. Most consensus groups have argued that fraction of inspired oxygen (F_{IO_2}) less than 0.4 is safe for prolonged periods of time and that F_{IO_2} greater than 0.80 should be avoided if at all possible.

Pulmonary Infectious Complications

Mechanically ventilated patients are at risk for pulmonary infections for several reasons. First, the natural glottic closure protective mechanism is compromised by an endotracheal tube. This permits continuous seepage of oropharyngeal material into the airways. Second, the endotracheal tube itself impairs the cough reflex and serves as an additional potential portal for pathogens to enter the lungs. This is particularly important if the circuit is contaminated. Third, airway and parenchymal injury from the underlying disease and from management complications makes the lung prone to infections. Fourth, the ICU environment, with its heavy antibiotic use and presence of very sick patients in close proximity, presents a risk for a variety of infections.

Preventing ventilator-associated pneumonias is critical because they greatly

affect length of stay and mortality. Hand washing, elevation of the head of the bed, oral care, and carefully chosen antibiotic regimens for other infections are beneficial. Management strategies that avoid breaking the integrity of the circuit (ie, changing the circuit only when it is visibly contaminated) also appear to be helpful. Continuous drainage of subglottic secretions is another simple way of reducing lung contamination with oropharyngeal material. Finally, aerosolized antibiotics in patients with purulent secretions can reduce the progression of tracheobronchitis to ventilator-associated pneumonia.

APPLYING MECHANICAL VENTILATORY SUPPORT

Tradeoffs Involved in Mechanical Ventilatory Support

To provide adequate support yet minimize VILI, the goals of mechanical ventilation must involve tradeoffs. Specifically, the need for potentially injurious pressures, volumes, and supplemental oxygen must be weighed against the benefits of gas exchange support. To this end, gas exchange goals have been examined over the last decade, and now pH goals as low as 7.15 and P_{O_2} goals as low as 55 mm Hg are often considered acceptable if such a strategy protects the lung from VILI. Together, these concepts embody “lung-protective” mechanical ventilation and guide current recommendations for the specific management of various forms of respiratory failure.

Considerations in Choosing Ventilator Settings for Different Forms of Respiratory Failure

Acute Lung Injury

Gas exchange abnormalities in acute lung injury (parenchymal injury) are a consequence of alveolar flooding or collapse, producing a maldistribution of ventilation that results in $\dot{V}/\dot{Q}$ mismatching and shunts. Because dead space ($\dot{V}/\dot{Q} = \infty$) is not a major manifestation of parenchymal lung disease unless there is very severe or end-stage injury, hypoxemia tends to be more of a problem than is carbon dioxide clearance in parenchymal lung disease.

Frequency-V_T settings for supporting parenchymal lung injury must focus on limiting end-inspiratory and tidal stretch. The importance of this strategy in improving outcome has been shown in numerous clinical trials, and these findings have led to widespread recommendations that in patients with acute

lung injury, the default V_T should be 6 mL/kg of ideal body weight (IBW) and the end-inspiratory lung distending pressure (P_{plat} corrected for any chest wall effects) should be less than 30 cm H_2O.

In recent years, the use of IBW to properly scale the V_T has been called into question. V_T based on IBW assumes a normal resting aerated lung size, something that clearly does not exist in severely injured lungs. This has given rise to the notion that V_T perhaps should be scaled to actual aerated lung size estimated by functional residual capacity determinations or imaging studies. A simple clinical approach to this might be to scale V_T to compliance (ie, smaller functional lungs are stiffer lungs) through the use of DP measurements (recall that DP = VT/Crs). Based on retrospective analysis, upper DP thresholds for producing VILI may be in the 14 to 16 cm H_2O range.

Conversely, increases in V_T settings above 6 mL/kg IBW might be considered if there is marked patient discomfort or suboptimal gas exchange, provided that the subsequent P_{plat} values (adjusted for C_{cw}) do not exceed 30 cm H_2O (or the DP remains low). Respiratory rate settings are then adjusted to control pH, and the I:E times are generally set in the physiological 1:2 to 1:4 range to ensure comfort and minimize air trapping.

Both mechanical and gas exchange approaches are available to set the PEEP-F_{IO_2} combination to support oxygenation while minimizing overstretch injury and oxygen toxicity. Mechanical approaches rely on the respiratory system pressure-volume relationships to set the PEEP and V_T. This can be assessed with a traditional static pressure-volume plot, a "slow-flow" single breath pressure-volume plot, a "best compliance" PEEP titration, or an airway pressure profile analysis during a constant flow breath ("stress index"). Conceptually, the goal is to provide ventilator settings between the overdistension and collapse-reopening points in the pressure-volume relationship. Unfortunately, these techniques are technically challenging and time consuming and thus are not used routinely in most patients.

Gas exchange criteria to guide PEEP and F_{IO_2} settings generally involve algorithms designed to provide adequate values for Pa_{O_2} (eg, 55-80 mm Hg) while minimizing P_{plat} and F_{IO_2}. Constructing a PEEP-F_{IO_2} algorithm is usually an empirical exercise in balancing P_{plat}, Pa_{O_2} (arterial oxygen saturation or oxygen saturation as measured by pulse oximetry), and F_{IO_2} and depends on the clinician's perception of the relative toxicities of high thoracic pressures, high

F_{IO_2}, and low arterial oxygen saturation. Two examples are given in **Table 3**. Several recent trials have compared a number of PEEP-F_{IO_2} algorithms in conjunction with low-V_T–limited-P_{plat} strategies. Taken together, these studies found that more aggressive PEEP strategies (ie, average 13-15 cm H_2O) can improve outcome in more severe disease with high recruitability potential, whereas more conservative PEEP strategies (ie, average 7-9 cm H_2O) are sufficient in less severely injured lungs with less recruitability.

In acute lung injury when gas exchange goals are not being met with conventional lung-protective strategies, 2 other mechanical ventilation approaches have received considerable attention in the last decade: (1) inverse ratio ventilation (I:E ratios of 2:1 to 4:1) with APRV and (2) HFV.

The concept underlying APRV is that the long inflation phase recruits more slowly filling alveoli and raises mean airway pressure without increasing applied PEEP (although intrinsic PEEP can develop with short deflation periods). Because spontaneous breathing can occur, patients do not need paralysis (unlike older forms of inverse ratio ventilation). Moreover, the additional spontaneous efforts during inflation can enhance both recruitment and cardiac filling compared with other controlled forms of support. These spontaneous efforts will add to the TPP during lung inflation. Clinical trials of APRV have shown that the mode provides reasonable gas exchange but have not shown that APRV improves clinically important outcomes.

HFV uses very high breathing frequencies (120-900 breaths per minute in the adult) coupled with very small V_T (usually less than anatomic dead space and often <1 mL/kg at the alveolar level) to provide gas exchange in the lungs. Gas transport under these seemingly unphysiological conditions involves such mechanisms as Taylor dispersion, coaxial flows, and augmented diffusion. The putative advantage to HFV is that the very small fluctuations in alveolar tidal pressure minimize cyclical overdistension and derecruitment while maintaining good recruitment with substantial mean airway pressures.

HFV has been shown in multiple neonatal and pediatric studies to reduce chronic lung disease. However, HFV trials in adults have had mixed results. Older, smaller studies suggested benefit, but 2 large recent trials showed either no benefit (OSCilation in ARDS [OSCAR] trial) or increased harm in HFV-treated patients (Oscillation for Acute Respiratory Distress Syndrome Treated Early [OSCILLATE] trial). Both of these trials, however, have been criticized for

having inexperienced clinicians operating unfamiliar devices, especially in patients with compromised cardiovascular function.

Obstructive Airway Disease

Respiratory failure from airflow obstruction is a direct consequence of increases in airway resistance. This leads to 2 important physiological changes. First, the increased pressures required for airflow can overload inspiratory muscles, producing a ventilatory pump failure with spontaneous minute ventilation inadequate for gas exchange (hypercapnic respiratory failure). Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal resting volume, and intrinsic PEEP is produced. These regions of overinflation create dead space and put inspiratory muscles at a substantial mechanical disadvantage, which further worsens muscle function. Overinflated regions can compress more healthy regions of the lung, impairing $\dot{V}/\dot{Q}$ matching. Regions of air trapping and intrinsic PEEP also function as a threshold load to trigger mechanical breaths.

Setting the frequency-V_T pattern in obstructive diseases involves many considerations that are similar to those used in setting these parameters in parenchymal lung injury. Specifically, V_T should be sufficiently low (eg, 6 mL/kg IBW) to ensure that P_{plat} values are less than 30 cm H_2O. As with parenchymal lung injury, V_T reductions should be considered to meet P_{plat} goals, and increases in V_T can be considered for comfort or gas exchange provided that P_{plat} values do not exceed 30 cm H_2O. The set rate is used to control pH. Unlike parenchymal disease, however, obstructive disease involves elevated airway resistance (and often the low recoil pressures of emphysema) that greatly increase the potential for air trapping, and this limits the range of breath rates available. Permissive hypercapnia may be an appropriate tradeoff to limit overdistension.

Because alveolar recruitment is less of an issue and overdistension is more of an issue in obstructive lung injury compared with parenchymal lung injury, more conservative PEEP strategies should be used for oxygenation support (eg, lower PEEP table in **Table 3**). A specific role for PEEP in the obstructed patient occurs when intrinsic PEEP serves as an inspiratory threshold load in the patient attempting to trigger a breath. Under these conditions, judicious application of circuit PEEP (up to 85% of intrinsic PEEP) can balance expiratory pressure throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.

Table 3. Two Variants of a PEEP-F_{IO_2} Table Used by the National Institutes of Health ARDS Network[a]

Lower PEEP/higher FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0		
PEEP	14	14	14	16	18	18-24		

Higher PEEP/lower FiO_2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16
FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0		
PEEP	18	20	22	22	22	24		

[a]One table emphasizes positive end-expiratory pressure (PEEP) over F_{IO_2}, and one emphasizes F_{IO_2} over PEEP. The targets are a P_{O_2} of 55-80 mm Hg and plateau pressure <30 cm H_2O. If the patient is below targets, move settings on table to right; if the patient is above targets, move settings on table to left.

Recovering Respiratory Failure: Weaning and Discontinuation

As respiratory failure stabilizes and begins to reverse, clinical attention shifts to ventilator withdrawal. Unfortunately, a number of large clinical trials have clearly demonstrated that current assessment and management strategies are not optimal and result in considerable undue delay in ventilator withdrawal. Increased length of stay, costs, exposure to pressure, and risk of infection result. Attempts to increase the aggressiveness of withdrawal, however, must be balanced against the risk of premature withdrawal with consequent airway loss, aspiration, and inspiratory muscle fatigue.

An evidence-based task force has recommended a daily assessment process for most patients requiring at least 24 hours of mechanical ventilator support:

1. Consider a patient a candidate for withdrawal if (a) the lung injury is stable

and resolving; (b) gas exchange is adequate with low PEEP and F_{IO_2} requirements; (c) hemodynamics are stable without a need for pressors; and (d) the patient can initiate spontaneous breaths.

2. In these patients, perform a spontaneous breathing trial (SBT, using T-piece, continuous positive airway pressure, or 5 cm H_2O pressure support) for 30 to 120 minutes. Assessments should include the ventilatory pattern, gas exchange, hemodynamics, and comfort. Patients who pass this trial should be considered for ventilator withdrawal.

3. Couple these efforts with aggressive strategies to reduce sedation.

In patients who pass the SBT, separate assessments are required to determine whether the artificial airway can be removed. These involve the evaluation of cough strength, suctioning frequency, and, to a certain extent, the ability to follow commands. Extubation failures can be expected in 10% to 20% of all extubations. Many of these involve airway protection, and thus prompt reintubation is indicated. However, in some patients, especially patients with chronic obstructive pulmonary disease with good airway protection, an extubation failure caused by increasing inspiratory muscle overload might be managed by noninvasive ventilation.

In patients who fail the SBT, a stable and comfortable level of interactive support should be provided until the next SBT. Frequent (eg, every 2-12 hours) support reductions between daily SBT considerations are usually not necessary. Indeed, support reduction strategies not only do not speed up the withdrawal process but also appear to excessively consume resources and unnecessarily expose the patient to muscle overload risks.

Over the years, a number of attempts have been made to automate the weaning process with feedback control algorithms designed to progressively reduce support. Approaches include mandatory minute ventilation (a synchronized intermittent mandatory ventilation mode with feedback reductions in mandatory breath rates), volume support, and adaptive support ventilation as described previously. The most recent approach also uses a volume support feedback strategy but incorporates respiratory frequency, end-tidal carbon dioxide, and an SBT reminder into the algorithm.

All of these strategies are based on the premise that support reduction between SBTs improves outcomes—a premise that, as noted, has no supporting evidence.

Because of this, studies evaluating these approaches have only been able to show that support reduction strategies can effectively be automated (with consequently less clinician work). However, no study has shown that any of these approaches shorten the duration of mechanical ventilation compared with strategies that mandate regular SBTs. The lone exception to this generalization might be in the postoperative setting where patient recovery is rapid and automated tools to assess this recovery might be helpful.

SUMMARY

Mechanical ventilatory support is a critical component of the management of patients with respiratory failure. However, this technology is supportive—not therapeutic. It cannot cure lung injury. Indeed, the best we can hope for is that ventilatory support will buy time by supporting gas exchange without harming the lungs.

Exciting innovations are on the horizon, but they must be assessed properly. This is particularly important for innovations with significant risks or costs. Only with properly conducted studies that include such clinically relevant outcomes as mortality, ventilator-free days, barotrauma, and costs can we effectively assess the sometimes bewildering array of new approaches to this vital life support technology.

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CHAPTER 22

Pulmonary Embolism and Pulmonary Hypertension in the ICU

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Key words: major pulmonary embolism, shock, thrombolytic therapy, pulmonary hypertension, acute respiratory distress syndrome, right-sided heart failure

PULMONARY EMBOLISM

An intensivist is most likely to be confronted with pulmonary embolism (PE) in two distinct clinical scenarios: first, a critically ill patient presenting to the ICU with undifferentiated shock or respiratory failure, and second, an established patient in the ICU or hospital who develops the constellation of signs and symptoms that indicate the possibility of PE. The diagnostic approach to either situation can be significantly challenging because PE may mimic many other life-threatening cardiopulmonary diseases, and a timely confirmatory diagnosis depends on the availability of diagnostic studies. Therapeutic anticoagulation or the use of thrombolytic therapy is often punctuated with great risk in critically ill patients, especially those with recent surgery or trauma. The first portion of this chapter discusses the diagnosis of PE in the ICU, resuscitation and stabilization of patients, and therapeutic management strategies.

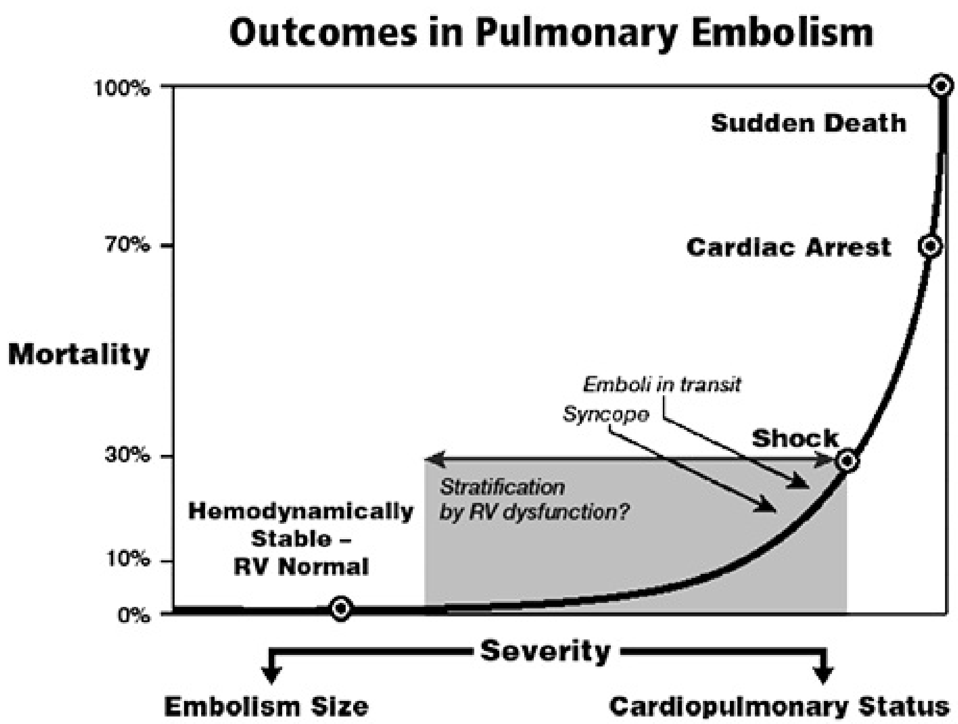
The incidence of PE in critically ill patients is difficult to determine given the multiple comorbidities in these patients. Signs and symptoms in this population may mimic or mask PE, oftentimes precluding a consistent diagnostic evaluation against the background of the decreasing frequency of autopsies in critically ill patients. A recent autopsy series, performed in the era of thromboprophylaxis, highlights the frequency of PE in critically ill patients. In this autopsy series of 600 patients, a clinical diagnosis of PE was suspected in 33 patients and confirmed in only 13 (39%). However, PE was discovered at autopsy in 73

patients, for an overall PE incidence of 14%. Most important, PE was determined to be the cause of death in 45% of the patients in whom PE was discovered only at autopsy and was a cause of death in 77% of the patients in whom PE was confirmed at autopsy. The investigators found that only recent abdominal surgery and the presence of renal failure were associated with a missed diagnosis. The population in whom PE was discovered only at autopsy had a higher frequency of septic shock. The investigators concluded that in an era dominated by either pharmacological or mechanical prophylaxis, critically ill patients remain at high risk for PE, which is a significant cause of death when the diagnosis is not suspected antemortem, as is frequently the case. Large observational and registry studies of PE indicate that the mortality remains significantly high, especially in those patients with hemodynamic instability likely admitted to an ICU. In the Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism (MAPPET) study, the overall 3-month mortality was 17%, which significantly increased to 31% when PE was associated with hemodynamic instability. In the hemodynamically unstable population, PE was reported to contribute to mortality in 91% of the patients. Similarly, high mortality rates in hemodynamically unstable patients were seen in the International Cooperative Pulmonary Embolism Registry (ICOPER) series, which reported a mortality of 51.9% in patients presenting with hemodynamic instability and a PE-attributable mortality of 63%.

The spectrum of outcomes in PE is depicted in **Figure 1**. The severity of PE is determined by the dynamic interplay between the patient's underlying cardiopulmonary status and the size of the embolus. The combination of embolism size and cardiopulmonary status that produces cardiac arrest is associated with a survivorship of approximately 70% in reported series. Given that approximately 30% of patients with cardiac arrest will survive the PE event, clinicians should continue chest compressions, which potentially can mechanically fracture the embolus, and consider the use of thrombolytic therapy and/or embolectomy. At the other extreme, the combination of embolus size and cardiopulmonary status that fails to precipitate right ventricular (RV) dilatation is associated with an exceedingly low mortality (0%-1%) when anticoagulation is appropriately instituted. Shock represents the failure of compensatory mechanisms to maintain forward flow and is associated with an approximate mortality of 30%. Hemodynamic instability may be consequent to a large embolus in a patient with normal cardiopulmonary status or may manifest with a smaller embolus against the background of impaired cardiovascular function. A substantial number of patients will present with RV dilatation and hemodynamic

stability and may range from a group on the cusp of shock to those with outcomes more closely aligned with a normal RV, as depicted in **Figure 1**. An evolving literature suggests that the use of biomarkers (brain natriuretic peptide [BNP], troponin) will assist in identifying patients at high risk for poor outcome in the hemodynamically stable population with RV dysfunction. As noted in **Figure 1**, syncope and emboli-in-transit are associated with higher mortality rates.

Figure 1. Outcomes in pulmonary embolism



Abbreviation: RV, right ventricle.

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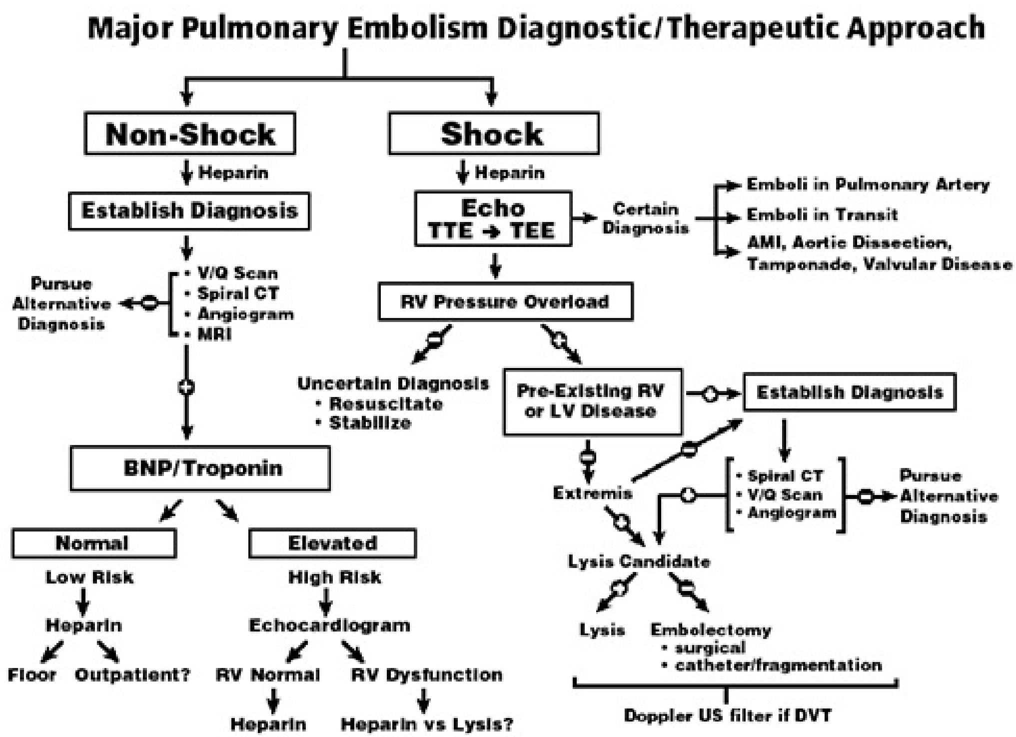
Diagnostic-Therapeutic Approach

Ensuring that PE is appropriately incorporated into the differential diagnosis of patients with undifferentiated shock or respiratory failure is predicated upon recognizing the footprint that PE leaves upon the physical examination and the readily available diagnostic studies. All critically ill patients should be considered at high risk for venous thrombolic events, especially patients with polytrauma, those who have undergone recent surgical procedures, and those

considered immobile in the ICU. Multiple risk factors are usually present and are additive in this population. An evolving literature suggests that patients with underlying liver disease are at increased risk for thromboembolic events, despite their coagulation abnormalities. On physical examination, findings that should increase the suspicion for PE include an elevated right artrial pressue (RAP) (occasionally with a dominant V wave indicative of tricuspid regurgitation), an increased second heart sound, an RV S_3, a pulsatile liver, and clinical findings suggestive of deep vein thrombosis in the extremities. In the patient with hemodynamic instability, the constellation of an elevated RAP with cool hypoperfused extremities against the background of relatively clear lungs on chest radiograph or by auscultatory findings localizes the hydraulic lesion to the RV with a differential diagnosis that should include PE. Readily available diagnostic studies should be reviewed for the footprint of PE. Electrocardiographic findings of right axis deviation and nonspecific ST-T segment abnormalities are common. Anterior T-wave inversions are reported to reflect the severity of the PE, and their resolution is correlated with successful thrombolytic therapy. A normal chest radiograph is unusual in PE, and large series have reported abnormalities to include consolidation, atelectasis, elevation of the hemidiaphragm, and vascular abnormalities suggestive of decreased perfusion. A normal PaO_2 does not effectively rule out PE. However, in patients with underlying disease, gas exchange abnormalities usually correlate with embolism size. Elevations in BNP and troponin are common in hemodynamically unstable PE. The former reflects RV cavitary dilatation and the latter correlates with subendocardial ischemia.

The presence of shock or hemodynamic instability has traditionally been used as a discriminator for determining outcomes and defining the diagnostic approach. **Figure 2** presents a diagnostic-therapeutic algorithm based on the presence or absence of shock. All patients presenting with suspected PE should receive anticoagulation during the course of their diagnostic evaluation provided there are no contraindications to full anticoagulation. In the critically ill patient, IV unfractionated heparin is preferable because of the potential variability in absorption of subcutaneous low-molecular-weight heparin in shock patients, the significantly shorter half-life of unfractionated heparin, and the ability to reverse the effects of unfractionated heparin by protamine sulfate in critically ill patients at high risk for bleeding.

Figure 2. Diagnostic-therapeutic approach to pulmonary embolism



Abbreviations: AMI, acute myocardial infarction; BNP, brain natriuretic peptide; CT, computed tomography; DVT, deep vein thrombosis; LV, left ventricle; MRI, magnetic resonance imaging; RV, right ventricle; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiography; US, ultrasound; $\dot{V}/\dot{Q}$, ventilation/perfusion.

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Computed tomography (CT) scanning has virtually supplanted ventilation-perfusion scanning, although the latter may still be used in patients who have renal insufficiency and are intolerant of a contrast dye load or young patients with a clear chest radiograph seeking to minimize radiation exposure. Traditionally, CT scanning has been reported only for the presence or absence of embolism. Recently, CT scanning has been used to define the severity and provide risk stratification of PE. An abnormally increased ratio of RV and left ventricular (LV) diameter measured on the transverse axis is associated with a significant odds ratio for all-cause mortality, PE mortality, and adverse outcomes. Although calculation of thrombus load and central location may be obtained via CT scanning, these are associated only with nonmortality adverse outcomes and are not predictive of all-cause mortality.

As illustrated in **Figure 1**, a subgroup of patients with hemodynamic stability and RV dysfunction are not in overt shock yet have mortality rates closely

approximating the shock population. An evolving literature suggests that the biomarkers BNP and troponin may be used to risk-stratify hemodynamically stable patients with RV dysfunction. BNP is crudely reflective of RV dilatation, and an elevated troponin level represents myocardial ischemia secondary to increased wall tension induced by PE. The absence of BNP elevation suggests the absence of RV dilatation and a stable course, whereas the combination of elevated BNP and troponin suggests a higher risk population. Although no controlled trials have examined the structured use of BNP and troponin to guide risk stratification therapy, it would seem reasonable that patients without a BNP elevation may be either discharged home or briefly admitted to the hospital. An isolated BNP elevation should warrant admission to the hospital, and those patients with both elevated BNP and elevated troponin levels require close observation along with serial trends in the clinical examination and troponin levels after admission.

Hemodynamic instability in a patient with suspected PE places the patient at high risk and necessitates an expeditious approach to diagnosis and treatment. As illustrated in **Figure 2**, echocardiography is an ideal first study in the initial assessment of a hemodynamically unstable patient. Although not confirmatory, the transthoracic echocardiogram (TTE) is helpful in defining other diseases that may mimic PE, and TTE can define the cardinal characteristics of RV dysfunction induced by PE. Findings on TTE that are suggestive of PE include RV cavity dilatation, an increase in the RV and LV diameter, bowing of the interventricular septum into the LV, pulmonary artery dilatation, and tricuspid regurgitation. Although RV dysfunction is classically associated with PE, RV dysfunction is not specific for PE. The absence of RV dilatation in a hemodynamically unstable patient effectively excludes PE as a cause of the shock presentation. Patients with underlying cardiopulmonary disease frequently show evidence of RV dilatation, and echocardiography cannot be used to effectively evaluate PE. As illustrated in **Figure 2**, a confirmatory study is needed to establish the diagnosis. The spiral CT scan has largely supplanted other confirmatory studies and is the study of choice for intensive care patients.

Resuscitation and Stabilization

Throughout the diagnostic evaluation period and in the early window after confirmatory studies, hemodynamically unstable PE patients frequently need aggressive resuscitation and stabilization. With worsening gas exchange, these patients often require intubation and mechanical ventilation. Because these

patients have marginal hemodynamic status, often maintained by a catecholamine surge, clinicians should undertake intubation judiciously using a conscious awake technique when possible and minimizing the effects of sedating agents on hemodynamics. After intubation, it is imperative to avoid further increases in the pulmonary vascular resistance by alveolar overdistension; this can occur with excessive hand ventilation, which is frequently tempting, given PE-induced increased dead space and elevated Pa_{CO_2}. Furthermore, this increase in respiratory rate or tidal volume may impair venous return, further jeopardizing RV function and precipitating cardiovascular collapse. Traditionally, several liters of crystalloid fluid have been used to resuscitate patients with PE-induced shock. However, with PE-induced RV dysfunction and dilatation, RV end-systolic wall stress is already appreciably increased. In the setting of RV dilatation and the bowing of the interventricular septum that is associated with elevated BNP and troponin levels, fluid resuscitation should be judiciously undertaken. Further RV dilatation will exacerbate the myocardial oxygen imbalance by increasing wall tension and will precipitate further RV dysfunction. Frequently, patients with hemodynamically unstable PE need vasoactive support. Increasing the mean arterial pressure (MAP) enhances the RV subendocardial coronary perfusion pressure gradient, which has been shown to enhance myocardial performance in animal models. Adrenergic agents such as norepinephrine have been found to be effective. Given the neurohumoral effects secondary to PE and the associated increase in pulmonary vascular resistance, several case reports have suggested the use of nitric oxide (NO) to decrease pulmonary vascular resistance and unload the RV.

Therapeutics

The presence of PE-induced shock or hemodynamic instability necessitates medical embolectomy with thrombolytic therapy or surgical embolectomy accomplished via catheter or the traditional surgical procedure. Multiple trials have been conducted with thrombolytic therapy in PE over the last 30 years. Virtually all studies that assessed the magnitude of embolic obstruction by using angiography and perfusion scans along with hemodynamic measurements or echocardiography reported a greater degree of embolic lysis with thrombolytic agents compared with heparin in the first 5 to 7 days. Recent meta-analyses of systemic thrombolytic therapy compared with heparin alone concluded that thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation, PE mortality, and PE recurrence but a significant risk of major hemorrhage and/or fatal intracranial bleeding. In

contrast to previous meta-analyses, the more recent meta-analyses found a positive mortality benefit in hemodynamically stable patients with RV dysfunction.

Hemodynamically unstable patients with PE who have contraindications to thrombolytic therapy or in whom thrombolytic therapy has failed should be considered for either surgical or catheter embolectomy. Historically, these procedures have been reserved for rescue treatment, although an evolving literature suggests that the indications for surgical or catheter embolectomy should be expanded. All patients with hemodynamic instability should be assessed for potential embolectomy because it is difficult to define which patients will fail thrombolytic therapy and may be candidates for embolectomy. The mortality and morbidity benefits of thrombolytic therapy must be weighed against the significant increase in bleeding. An evolving literature supports the use of catheter-directed embolectomy for acute PE with and without hemodynamic instability to achieve the clinical benefits without the risk of significant bleeding at specific centers with defined expertise.

Placement of an inferior vena cava filter has been retrospectively validated as beneficial in hemodynamically unstable patients receiving thrombolytic therapy or surgical embolectomy. Conversely, placement of prophylactic inferior vena cava filters in hemodynamically stable high-risk patients (active cancer, chronic cardiac or respiratory disease, ischemic stroke with paralysis, deep vein thrombosis with iliocaval involvement or evidence of RV function and/or myocardial injury) provides no benefit in terms of recurrent PE, symptomatic deep vein thrombosis, major bleeding, or death.

Summary for Pulmonary Embolism

PE in the ICU remains challenging because of the comorbidities in critically ill patients that may mask or mimic the signs and symptoms of PE, logistical challenges in securing diagnostic studies, and the ever-present risk of hemorrhage with heparin or thrombolytic therapy. Understanding the pathophysiological process of PE enables clinicians to use physiological risk stratification to assist in diagnostic and therapeutic management strategies. Echocardiography is an ideal study to assess RV function in the hemodynamically unstable patient. CT scanning can be used to confirm or exclude PE and assist with risk stratification. Hemodynamically unstable PE is a medical emergency that necessitates medical embolectomy with thrombolytic therapy or surgical or catheter embolectomy.

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is a disorder of the pulmonary vasculature that is characterized by an increased pulmonary artery pressure and secondary RV failure. PH is indicated by mean pulmonary artery pressure of 25 mm Hg or more at rest. Recognition of PH in the critically ill patient is essential, as the presence of PH affects the ICU course through impaired function of the right side of the heart and decreased cardiac output.

Many disorders in the ICU are complicated by PH (**Table 1**). PH can be idiopathic or associated with a variety of disorders and is broadly classified into 5 groups based on shared pathophysiological and clinical features (**Table 2**). Although describing most patients with PH, this classification system does not encompass all the forms of PH seen in the ICU. To this classification system other causes must be added, including acute PE, acute respiratory distress syndrome (ARDS), and complications associated with cardiothoracic surgery. Although supportive care is similar for all forms of PH, defining the primary cause is essential, because specific treatment depends on the underlying process.

Table 1. Conditions That Cause Pulmonary Hypertension (PH) in the ICU

Worsening of preexisting PH
Pulmonary arterial hypertension (idiopathic, connective tissue disease related, heritable)
PH due to chronic disease of the left side of the heart (ischemic or nonischemic cardiomyopathy, valve disease)
PH due to chronic obstructive pulmonary disease, interstitial lung disease
PH due to chronic hypoventilation (obstructive sleep apnea, obesity hypoventilation syndrome, neuromuscular disorders)
Chronic thromboembolic disease
Portopulmonary hypertension
Acute left-sided heart disease
Myocardial infarction
Postpartum cardiomyopathy
Drug or toxin
Acute lung injury
Acute respiratory distress syndrome
Ventilator-induced PH (increased airway pressures)
Acute pulmonary embolism
Postoperative PH
Coronary artery bypass grafting
Heart transplant
Lung transplant
Pneumonectomy
Sepsis

Acute chest syndrome (sickle cell disease)	
Volume overload Renal failure	

Table 2. Classification of Pulmonary Hypertension (Fifth World Symposium, 2013)

PH Group	Subtypes	Specific Examples
Group I: PAH	Idiopathic or inherited PAH	
	Drug- and toxin-induced PAH	Anorexigens, methamphetamines
	Conditions associated with PAH	Collagen vascular diseases Congenital systemic to pulmonary shunts Portal hypertension HIV infection
Group II: PH due to left-sided heart disease	Left ventricle dysfunction, valve disease	
Group III: PH due to lung diseases	Chronic obstructive pulmonary disease	
	Interstitial lung disease	
	Sleep-disordered breathing, hypoventilation	Obstructive sleep apnea, obesity hypoventilation syndrome, neuromuscular disorders
Group IV: chronic thromboembolic PH	Chronic thromboembolic PH	
Group V: PH with unclear mechanisms		Myeloproliferative disorders, sarcoidosis, chronic hemolytic anemia

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

Information taken from Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D42-D50.

Pathophysiological Characteristics

The normal pulmonary circulation, a low-resistance, high-capacitance circuit, is

capable of accommodating the entire cardiac output at perfusion pressures that are significantly lower than those of the systemic circulation. Accordingly, the RV is a thin-walled muscle with limited contractile reserve. In contrast to normal pulmonary vascular functioning, PH can be caused by narrowing of the precapillary vessels (arteries and arterioles), loss of vascular surface area, and/or passive pressure from the postcapillary vessels (**Table 3**). In pulmonary arterial hypertension (PAH, group I PH), vascular remodeling occurs secondary to abnormal proliferation of smooth muscle cells and fibroblasts. The molecular pathways responsible for these changes in idiopathic PAH include reduced expression of pulmonary endothelial NO synthetase and prostacyclin synthetase and increased levels of endothelin 1 and thromboxane. In PH secondary to left-sided heart disease (group II PH), passive venous congestion is the primary disorder, although vascular remodeling and pulmonary artery vasoconstriction may occur over time and lead to a further increase in pulmonary pressures. In those with chronic lung disease, PH develops as a consequence of chronic hypoxia and destruction of the pulmonary vasculature.

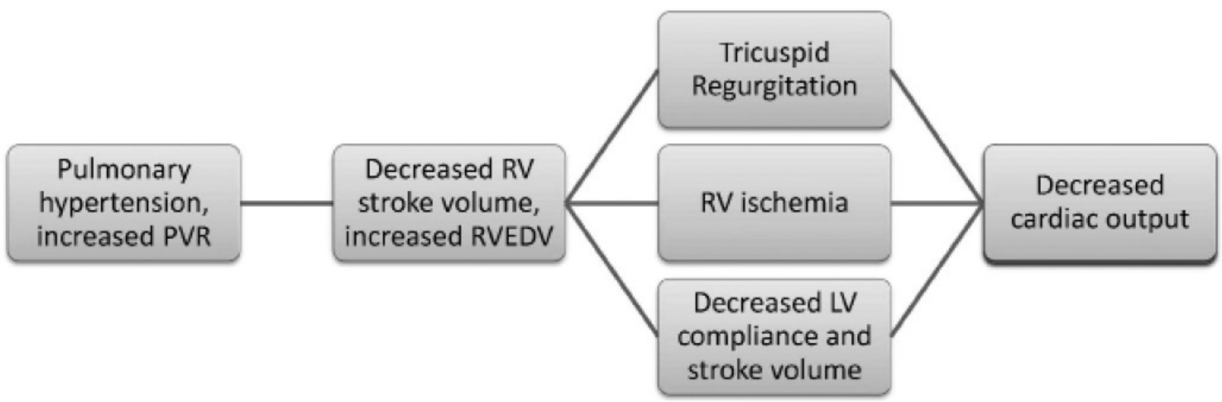
Table 3. Vascular Lesion Location, Pathological Process, and Corresponding Forms of Pulmonary Hypertension

Vascular Lesion Location	Pathological Process	Corresponding Form of Pulmonary Hypertension
Precapillary	Intravascular obstruction or vascular remodeling	Idiopathic; drugs or toxins; connective tissue disease; pulmonary emboli
Capillary	Destruction or mechanical or physical obstruction of capillary bed	Emphysema; interstitial lung disease; increased airway pressures or positive end-expiratory pressure; pneumonectomy
Postcapillary	Passive from elevated left atrial pressure	Left ventricular failure; valve disease

In addition to experiencing exacerbation of the previously discussed chronic disorders, critically ill patients may manifest acute PH due to other causes. ARDS can result in PH through pulmonary vasoconstriction, thromboembolism, and interstitial edema and can be exacerbated through the elevated airway pressures of positive pressure ventilation. Sepsis can result in PH through cardiac dysfunction and increased pulmonary vasoconstriction. Finally, in those with acute PE, mechanical obstruction of the proximal pulmonary arteries by thrombus can result in acute elevations in pulmonary artery pressures.

Regardless of the cause of PH, the final common pathway for its progression in critically ill patients is right-sided heart failure. The time course of the development of PH dictates the ability of the RV to adapt to the increased pulmonary artery pressures. With acute elevations in afterload, the unconditioned RV suffers an abrupt decrease in stroke volume. Although an increase in RV end-diastolic volume (RVEDV) may transiently improve stroke volume through the Frank-Starling mechanism, additional increases in RVEDV further reduce global cardiac output due to RV ischemia, tricuspid regurgitation, and ventricular interdependence. The latter phenomenon occurs because the shared ventricular septum is pushed to the left in circumstances of elevated RVEDV, decreasing both LV compliance and stroke volume and further reducing overall cardiac output. The sum result of progressive PH and RV failure is decreased RV stroke volume, increased RVEDV, and decreased cardiac output, resulting in the clinical presentation of systemic venous congestion and cardiogenic shock (**Figure 3**).

Figure 3. Pathophysiological process of right-sided heart failure in critical illness–related pulmonary hypertension



Increased pulmonary vascular pressure, regardless of cause, results in increased right ventricular (RV) afterload and decreased RV stroke volume. The compensatory increase in RV end-diastolic volume (RVEDV) may transiently improve cardiac output, but if RV afterload continues to increase, progressive increases in RVEDV will be counterproductive; the increased RV diameter causes tricuspid regurgitation and increases RV wall tension, promoting RV ischemia. Increased RVEDV also impairs left ventricular (LV) compliance and stroke volume due to the shared intraventricular septum, which is pushed to the left by elevated RV filling volumes. All of these consequences of increased pulmonary vascular resistance (PVR) and RVEDV eventually reduce overall cardiac output and lead to RV failure.

Diagnosis

Examination findings that are suggestive of PH include distended jugular veins,

an RV heave in the parasternal area, an increased P_2 component of the second heart sound, and the murmur of tricuspid regurgitation at the lower right sternal border. Hepatomegaly, ascites, and lower extremity edema are systemic findings of right-sided heart failure. Chest radiographs are not generally useful in detecting PH. The electrocardiogram may show changes of RV hypertrophy or right axis deviation. Several biomarkers, including troponins and natriuretic peptides, may be elevated in PH, but they lack specificity and also are increased in patients with left-sided heart disease or renal insufficiency.

TTE with Doppler estimation of pulmonary arterial pressures is the initial study of choice in evaluating patients with symptoms suggestive of PH. Two-dimensional TTE can assess for changes consistent with RV overload, such as right atrial enlargement, RV hypertrophy or dilation, or systolic bowing of the interventricular septum toward the LV. TTE also provides evidence of LV and valve function that can provide clues to the cause of PH. Doppler echocardiography is the standard means by which to estimate pulmonary pressures. The most common method used to estimate systolic pulmonary artery pressure (sPAP) is based on the measurement of the tricuspid regurgitant jet velocity (TRV, in meters per second) and an echocardiographic estimation of RAP. Using a modified Bernoulli equation (sPAP ≈ 4(TRV)2 + RAP), clinicians can consider PH to be present when the estimated sPAP is 40 mm Hg or higher or the TRV is 3.0 m/s or higher. An indicator of RV systolic function that has been validated and is easily obtained by routine TTE is that of tricuspid annular plane systolic excursion (TAPSE). This measurement is based on the fact that the RV systolic excursion occurs predominantly in a longitudinal axis. A reduced RV systolic function is therefore correlated with a reduced TAPSE distance. In patients with PAH, a TAPSE of 1.8 cm or less has been associated with reduced cardiac index and worse survival.

Right-sided heart catheterization (RHC) remains the gold standard by which to diagnose PH. Measurements obtained by RHC include RAP, pulmonary artery pressure, pulmonary arterial occlusion (wedge) pressure, venous oxygen saturations, and cardiac output. Several limitations may complicate use of RHC in critically ill patients. Changes in intrathoracic pressure induced by positive pressure ventilation will affect hemodynamic measurements; care must be taken to ensure that all measurements are obtained at end-expiration. In addition, accurate assessment of cardiac output may be challenging. Thermodilution methods may be confounded by low cardiac output or tricuspid regurgitation, whereas Fick methods may be inaccurate if oxygen consumption is assumed,

rather than calculated, in a critically ill patient.

Controversy surrounds the use of pulmonary artery catheters in critically ill patients, and studies have failed to demonstrate a mortality benefit through the use of these catheters. Although indirect assessments of cardiac output and fluid responsiveness have been proposed, these techniques have not been validated in patients with right-sided heart failure.

Management

General Considerations

Most of the following interventions either have not been studied in large randomized trials or have been restricted to patients with PAH (group I PH). Therefore, many of these treatments are based on expert recommendation rather than evidence-based medicine.

When a specific cause of PH and RV failure is known, measures directed at the underlying process should be implemented. However, regardless of the cause, general supportive care is similar for all PH patients: volume optimization, RV afterload reduction, and increased RV contractility. These treatment goals can be achieved through a combination of interventions, including hemodynamic monitoring, selective use of vasopressor and inotropic agents and pulmonary vasodilators, and mechanical support and surgical interventions (**Table 4**).

Table 4. General Approach to the Treatment of Pulmonary Hypertension and Right-Sided Heart Dysfunction in Critically Ill Patients

Target of Intervention	Physiological Goals	Specific Examples
Intravascular volume	• Optimize filling of RV to increase preload and stoke volume. • Avoid overdistension of RV, which will reduce LV compliance, stroke volume via intraventricular dependence.	• Administer a fluid challenge to increase overall cardiac output. • Monitor RV filling and cardiac output by noninvasive (echocardiography) or invasive (right-sided heart catheter) methods. • Monitor systemic perfusion via mixed venous oxygenation saturation.
RV afterload	• Reduce pulmonary vascular	• Avoid hypoxic pulmonary

	pressure and resistance.	vasoconstriction via adequate oxygenation. • Minimize airway pressures and positive end-expiratory pressure, both of which increase RV afterload. • Avoid vasopressors that increase pulmonary vascular tone, such as phenylephrine. • Maintain Pa_{CO_2} and pH near normal, as acidemia increases pulmonary vascular tone. • Selectively use pulmonary vasodilators, such as nitric oxide.
RV contractility	• Increase RV inotropy.	• Selectively use inotropic agents to increase cardiac output, such as dobutamine.

Abbreviations: LV, left ventricle; RV, right ventricle.

Volume Balance

Volume balance is crucial in patients with PH and RV impairment. Both hypovolemia and hypervolemia will result in reduced cardiac output; too little preload will reduce RV stroke volume whereas too much volume will shift the intraventricular septum to the left, impairing LV compliance and cardiac output. Establishing the optimal fluid balance can be challenging in critically ill patients, and no "goal" central venous filling pressure has been established that is applicable to all patients. Instead, volume challenges should be administered in conjunction with invasive or noninvasive measures of cardiac output (eg, echocardiography or RHC); volume should be administered only until filling pressures continue to rise but cardiac output plateaus. Conversely, diuretics should be considered if RV dilation is present in the setting of volume overload.

Mechanical Ventilation

Intubation of those with PH should be undertaken cautiously. Patients with impaired RV function are volume sensitive; the use of vasodilating induction agents, such as propofol, may precipitate cardiovascular collapse in these patients. Furthermore, hypoxia is a potent pulmonary vasoconstrictor and will increase RV afterload. If endotracheal intubation is required in critically ill patients with PH, preference should be given to the use of awake intubation

techniques to minimize hypotension and hypoxia. If rapid-sequence intubation is clinically mandated, careful selection and dose of induction agent (eg, etomidate or ketamine) may reduce the risk of hypotension.

Positive pressure ventilation has potential negative effects on the pulmonary vascular system. Increased intrathoracic pressure will reduce venous return to the right side of the heart. Furthermore, increased airway pressures will increase pulmonary vascular resistance and RV afterload. In addition to the direct hemodynamic impact of positive pressure ventilation, the use of low-tidal-volume ventilation and permissive hypercapnia may be detrimental in patients with RV failure. The respiratory acidosis that accompanies hypercapnia in the range typically tolerated in patients with ARDS results in increased pulmonary vasoconstriction and RV afterload. Moreover, both high and low lung volumes will increase RV afterload due to the competing effects of intra-alveolar and extra-alveolar vessels; pulmonary vascular resistance is minimized at a resting lung (functional residual) capacity. Thus, the optimal strategy for managing patients with RV failure should include tidal volumes and positive end-expiratory pressure levels that approximate resting lung capacity and minimize airway pressures while allowing adequate oxygenation. Permissive hypercapnia should be avoided given its tendency to worsen pulmonary vasoconstriction.

Vasopressors and Inotropes

Many critically ill patients with PH will require vasoactive medications for hemodynamic support. Unfortunately, few studies have explicitly investigated the actions of systemic vasopressors or inotropes in critically ill patients with RV failure. The literature that is available is a mix of animal and human studies; the results of these investigations are summarized in **Table 5**. Dobutamine and milrinone have the most favorable effects on RV function, with reductions in pulmonary vascular resistance and increased cardiac output. However, both of these agents tend to reduce MAP and can worsen ventilation-perfusion matching. Norepinephrine and vasopressin at low to moderate doses have minimal effects on the pulmonary vasculature while also increasing MAP. Phenylephrine has negative effects on right-sided heart function and should be avoided in patients with RV failure. In practice, many of these agents are used in combination to maximize cardiac output while also maintaining MAPs.

Table 5. Effects of Vasoactive Agents on the Pulmonary and Systemic Circulations

Agent	Effect on Pulmonary Vascular Resistance	Effect on Cardiac Output	Effect on Systemic Mean Arterial Pressure

Dobutamine	↓	↑↑	↓
Milrinone	↓	↑↑	↓
Norepinephrine	None to ↑	↑	↑↑
Vasopressin	None to ↑	None to ↑	↑
Phenylephrine	↑↑	↓	↑↑

Pulmonary Vasodilators

Remarkable progress has been made in elucidating the molecular pathways involved in the pathogenesis of PH, which has led to a greater understanding of the pulmonary vascular system and treatment advances. Most of the currently approved therapies, which target the prostacyclin, NO, or endothelin pathways, are indicated only for those with group I PH (PAH). Most of the available pulmonary vasodilators have not been rigorously studied in the ICU.

Of the available pulmonary vasodilators, inhaled NO has been the most widely studied in the critically ill population. NO acts on the vascular smooth muscle, activating soluble guanylate cyclase and mediating vasodilation. NO has a brief half-life and its effects are predominantly local. Administered as a gas, NO preferentially vasodilates the ventilated pulmonary vasculature, resulting in both reduced pulmonary vascular resistance and improved ventilation-perfusion matching, with a resultant increase in oxygenation. NO has been shown to decrease pulmonary artery pressures in multiple disorders, including ARDS, PAH, and postoperative PH, although no study to date has demonstrated a mortality benefit of NO. The use of NO has rarely been associated with methemoglobinemia and renal failure. Caution must be used in weaning patients from inhaled NO, as rebound PH and cardiovascular collapse can occur.

The prostacyclins, another class of pulmonary vasodilators, act via adenylate cyclase to induce vasodilation. Epoprostenol is an intravenous prostacyclin with potent pulmonary vasodilator properties and a short duration of action. Epoprostenol has demonstrated a mortality benefit in PAH patients and is the agent of choice to treat decompensated right-sided heart failure due to PAH. However, little evidence is available to support the use of epoprostenol outside of the PAH population. Like NO, inhaled prostacyclins are selective pulmonary vasodilators in ventilated regions of the lung that avoid the systemic hypotension and intrapulmonary shunting that plague parenteral prostacyclins. Several

prostacyclins, including iloprost and treprostinil, are available as aerosolized formulations. Inhaled epoprostenol is being used increasingly in critically ill patients as an alternative to inhaled NO, with similar reported improvements in pulmonary artery pressure and cardiac output. Although appealing, the use of inhaled prostacyclins in critically ill patients is limited by a lack of robust clinical trial evidence.

The remaining pulmonary vasodilators, all of which are indicated for use in group I PH (PAH), are long-acting oral agents in either the phosphodiesterase 5 inhibitor class (sildenafil, tadalafil, vardenafil), the endothelin receptor antagonist class (bosentan, ambrisentan, macitentan), or the recently introduced soluble guanylate cyclase stimulator class (riociguat). The use of these agents in critically ill patients remains case-based only. Moreover, in addition to having a prolonged duration of action, these agents raise concern in the ICU because of their potential to adversely affect gas exchange and systemic blood pressure. Therefore, the use of these oral medications in critically ill patients with right-sided heart failure should be limited to clinical trials.

Mechanical Support and Surgical Treatment

Although medical therapy is the cornerstone of treatment of PH, some forms of progressive PH and right-sided heart failure can be treated by mechanical support or surgery. Mechanical support in the form of venoarterial extracorporeal membrane oxygenation is sometimes used in patients with refractory right-sided heart failure, usually as a bridge to RV recovery or transplantation. RV assist devices can be used to support isolated RV failure, but these devices are generally contraindicated in right-sided heart failure associated with significant PH.

The type of surgical intervention for refractory PH depends on the underlying cause and the patient's probability for eventual recovery or transplantation. The treatment of choice for patients with chronic thromboembolic PH (group IV PH) is pulmonary endarterectomy, a procedure that can cure pulmonary vascular disease in selected patients. Patients with refractory or progressive PH may be candidates for the salvage procedure of percutaneous balloon atrial septostomy. Atrial septostomy decompresses the RV via the creation of a right-to-left interatrial shunt, decreasing filling pressures in the right side of the heart and improving cardiac output and systemic oxygen delivery at the expense of decreased arterial oxygen saturation. Finally, transplantation, either lung or both heart and lung, is the definitive treatment option for those with PH who are not

responding to medical therapy. Patients should be referred to a transplant center when medical therapy fails or they have hemodynamic parameters associated with a poor prognosis (cardiac index <2 L/min/m^2 or mean RAP >15 mm Hg).

Summary for Pulmonary Hypertension

PH is commonly encountered in critically ill patients and may represent worsening of preexisting disease or may occur secondary to another disorder, such as ARDS or acute PE. Although specific therapy is available for progressive PAH, most of the treatment for other forms of critical illness–related PH is supportive. In particular, attention must be paid to optimizing volume status, reducing RV afterload, and increasing RV inotropy. Mechanical support of the failing RV may be an option in some patients with progressive PH. Finally, the hemodynamic impact of positive pressure ventilation in those with PH must be appreciated.

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CHAPTER 23

Hemoptysis, Pneumothorax, and Inhalational Injuries

Scott E. Kopec, MD, FCCP, and Marie T. Mullen, MD

Key words: hemoptysis, pneumothorax, inhalational injuries

This chapter brings together 3 dissimilar disease processes—hemoptysis, pneumothorax, and inhalational injuries. These conditions commonly are encountered in the critical care environment and carry significant morbidity and mortality. All 3 entities require rapid identification and intervention.

HEMOPTYSIS

Hemoptysis is the expectoration of blood. Hemoptysis can range from scant amounts of blood loss to massive, life-threatening quantities. Conservatively treated, massive hemoptysis can have up to an 85% risk of mortality. When initiating care, clinicians must focus first on stabilization of the patient. The term *massive hemoptysis* is defined as the expectoration of blood in quantities sufficient to be life threatening. The general consensus is that massive hemoptysis involves the expectoration of either more than 600 mL of blood in 24 hours or more than 100 mL of blood in 1 hour. The time period in which the hemoptysis occurs is as important as the amount: A higher amount in a short period of time is associated with the highest mortality. Mortality depends not only on the blood volume and rate of bleeding but also on the extent of underlying disease and the patient's ability to clear secretions or blood. Such considerations contribute to defining massive hemoptysis by magnitude of effect as opposed to volume alone.

Causes for massive hemoptysis are summarized in **Table 1**. Bronchiectasis, tuberculosis, mycetomas, and bronchogenic malignancy account for the majority of cases. Bronchiectasis and lung carcinoma are the leading causes worldwide.

The bronchopulmonary circulation is significantly complex and variable among individuals. The majority of bleeding in massive hemoptysis originates from the systemic arteries, primarily the high-pressure bronchial arteries. The pulmonary arteries may be the source in only 5% of cases, and these cases tend to be due to infectious or inflammatory sources. Bleeding tends to be more significant when coming from the systemic arteries because of higher pressures. Any bleeding originating from the systemic and bronchial arteries, even mild, has the propensity to cause life-threatening hemoptysis.

Table 1. Causes of Massive Hemoptysis

Infectious • Mycobacteria, particularly tuberculosis • Fungal infections (mycetoma) • Lung abscess • Necrotizing pneumonia (*Klebsiella, Staphylococcus, Legionella*) • Endocarditis with septic emboli	**Parasitic** • Hydatid cyst • Paragonimiasis
Pulmonary • Bronchiectasis (including cystic fibrosis) • Chronic bronchitis • Emphysematous bullae • Alveolar hemorrhage and underlying causes	**Trauma** • Blunt or penetrating injury • Suction ulcers • Tracheoarterial fistula
Neoplastic • Bronchogenic carcinoma • Bronchial adenoma • Pulmonary metastases • Sarcoma	**Coagulopathy** • Von Willebrand disease • Hemophilia • Anticoagulant therapy • Thrombocytopenia • Platelet dysfunction • Disseminated intravascular coagulation
Iatrogenic • Swan-Ganz catheterization • Bronchoscopy • Transbronchial biopsy • Transtracheal aspirate	**Vasculitic** • Behçet disease • Wegener's granulomatosis • Goodpasture syndrome • Systemic lupus erythematosus
Vascular • Pulmonary infarct or embolism • Mitral stenosis • Arteriobronchial fistula • Arteriovenous malformations • Bronchial telangiectasia	**Hemoptysis in children** • Bronchial adenoma • Foreign body aspiration • Vascular anomalies **Miscellaneous** • Lymphangioleiomyomatosis

• Left ventricular failure **Drugs and Toxins** • Penicillamine • Solvents • Crack cocaine • Trimellitic anhydride • Bevacizumab	• Endometriosis • Pneumoconiosis • Broncholith • Lung transplantation • Cryptogenic

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When one is assessing a stable patient with massive hemoptysis, the history and physical examination may be helpful in determining the cause of hemoptysis, the status of pulmonary function, and the possibility of underlying chronic lung disease. Key questions pertain to smoking history; previous episodes of hemoptysis; existing lung, cardiac, or renal disease; presence of skin lesions; tuberculosis exposure; and recent anticoagulation.

Other information that is important in the ICU patient is a history of a recent tracheostomy (which might suggest the presence of a tracheoinnominate fistula) and the presence of a Swan-Ganz catheter (which might suggest a pulmonary artery rupture). The clinician should also exclude nonpulmonary sources such as pseudo-hemoptysis from the nasopharynx, oropharynx, or gastrointestinal tract. Inspection of the nasopharynx and mouth should be routine. Some common traits of true hemoptysis include frothy quality, clotted or liquid appearance, bright red color, alkaline pH, and expectorated blood mixed with sputum. Patients usually will have dyspnea, hypoxemia, and a cough, but anemia and melena are not common. In unstable patients with massive hemoptysis, a complete history and physical examination should be delayed until the patient is stabilized. Although the history and physical examination may play a crucial role in determining the cause of bleeding, they are rarely helpful for localizing the bleeding.

Management of massive hemoptysis should be approached in 3 steps: Immediately focus on stabilization of the airway in conjunction with circulation, localize the source of the bleeding, and determine therapeutic options to stop the bleeding. Massive hemoptysis typically involves a multidisciplinary approach between intensive care, anesthesia, thoracic surgery, interventional pulmonology, and interventional radiology staff.

Stabilization of the Patient

Fatalities from hemoptysis occur from asphyxiation as blood fills and obstructs the central airways. The central airways have an estimated volume of 150 mL. Rapid accumulation of blood and clot can overcome a patient's cough and mucociliary clearance capacity. The initial priority should be to stabilize the patient and protect the airway. If the bleeding is known to be localized to one lung, the patient should be placed in the lateral decubitus position with the affected or "bad" lung down to minimize contralateral spillage of blood into the unaffected or "good" lung. A patient with massive hemoptysis should be intubated if the patient is in respiratory distress, is unstable hemodynamically, or demonstrates rapidly progressing hemoptysis.

If feasible, a rapid oral examination of the patient should be considered prior to intubation to assess for potential sources of bleeding. The fiberoptic bronchoscope is the preferred method of intubation if the clinical situation permits. The fiberoptic bronchoscope permits evaluation of the subglottic region and proximal trachea for bleeding prior to intubation. Emergent circumstances may not permit this evaluation. The patient should be intubated with a large-bore endotracheal tube (size 8-8.5 for females and size 8.5-9 for males). Nasotracheal intubation is not recommended. Using a fiberoptic bronchoscope to intubate a patient with massive hemoptysis may allow for localization of the bleeding and therapeutic intervention in addition to stabilization of the airway.

If active bleeding can be isolated to one mainstem bronchus or beyond, selective lung intubation into the unaffected lung can be performed. Although this procedure can be performed blindly into the right mainstem bronchus in a patient with bleeding from the left lung, selective intubation into the left mainstem bronchus typically requires expertise with fiberoptic guidance. Bronchoscopic guidance is recommended regardless of location, as a common complication of blind right mainstem intubation is occlusion of the right upper lobe from the endotracheal tube.

Selective bronchus intubation allows for only unilateral ventilation. An alternative to unilateral intubation is the use of a specialized endobronchial blocking device.

A double-lumen endotracheal tube can be used as an alternative device to secure the airway. Theoretically, the device permits ventilation of both lungs while protecting the uninvolved lung from aspiration. However, use of a double-lumen tube is associated with significant potential problems and some authors

discourage this technique. Double-lumen endotracheal tubes are difficult to place. The small lumen size prohibits passage of a therapeutic bronchoscope or a large suction catheter, and the tube can be obstructed by clots.

Other important aspects of initial stabilization include vascular access, volume resuscitation, correction of existing coagulopathy, supplemental oxygen and ventilatory support, and cough suppression. Cough suppression includes the use of opioids to limit shear forces in the airway. Pertinent tests include a coagulation profile, blood type and crossmatch, and chest radiograph in addition to standard blood work.

Localizing the Source of the Bleeding

After the initial stabilization, location of the site of bleeding is pivotal. For patients with massive hemoptysis, flexible bronchoscopy should be considered the procedure of choice in an attempt to localize the bleeding. Advantages of flexible bronchoscopy include its availability, ability to be performed bedside, high success in localizing bleeding, and compatibility with simultaneous interventions to stop bleeding. Some of the limitations of flexible bronchoscopy for massive hemoptysis include poor visualization, difficulty clearing the airways of clots, and difficulty oxygenating and ventilating the patient during the procedure. In these cases, rigid bronchoscopy should be considered. Rigid bronchoscopy allows for airway protection, better clearance of the airways, and better ability to ventilate and oxygenate the patient during the procedure. Rigid bronchoscopy also provides a larger working channel for procedures and interventions. Rigid bronchoscopy is particularly advantageous for the management of actively bleeding tracheal tumors or associated obstructing airway lesions. Disadvantages of a rigid bronchoscopy include inability to evaluate the distal airways and the need to perform the procedure under general anesthesia in the operating room. Flexible bronchoscopy can be combined with rigid bronchoscopy by inserting the flexible scope through the rigid scope to enhance distal visualization. Bronchoscopy should be performed as soon as possible and can successfully localize the source of massive hemoptysis in 67% to 93% of patients. Visualization of clots within the airways is inadequate in localizing the bleeding, as one needs to find active bleeding.

For patients with nonmassive hemoptysis, the timing of bronchoscopy remains controversial. Early bronchoscopy is more likely to identify the source, as opposed to a delayed approach, but the timing of the procedure may not change management decisions or outcome.

Chest computed tomography (CT) may be an adjunct and in some cases an alternative to bronchoscopy in localizing bleeding in patients with massive hemoptysis. Conditions such as bronchiectasis, lung abscesses, arteriovenous malformations, and tumors may be better visualized by chest CT than by bronchoscopy. The major disadvantage of a chest CT is that the potentially very unstable patient needs to be moved out of the ICU for the test. If bronchoscopy is not readily available, chest CT should be considered the next option in attempting to localize the source of the bleeding. Angiography typically is performed after the source of bleeding has been localized by bronchoscopy or chest CT and usually is not used as the initial procedure to localize bleeding. Potential indications for performing an angiography first include known arteriovenous malformations or ruptured pulmonary artery from a Swan-Ganz catheter. Although limited, chest radiography has identified the source of bleeding in up to 35% of cases, particularly in presentations involving tumors or tuberculosis.

Treatment Options for Massive Hemoptysis

Treatment options can be divided into temporary and definitive. The goal of temporary treatment is to help stabilize the patient, whereas the goal of definitive treatment is to eliminate the cause. Multiple temporary treatment options are available. Direct mechanical choices include balloon tamponade of the airway with a specific endobronchial blocker balloon. Topical options include using iced saline lavage and instilling topically acting vasoconstrictors or coagulants. All of these treatments typically are performed concurrently during the initial bronchoscopy to localize bleeding. Balloon tamponade can be used in the segment or subsegment that is bleeding; the balloon can remain inflated for 24 to 48 hours. Iced saline lavage consists of irrigating the area of bleeding with 50-mL aliquots of cold saline. The cold saline results in vasoconstriction and reduced blood flow. An average volume of 500 mL may be needed to control bleeding. Topical vasoconstrictors such as epinephrine (1:20,000 dilution, 5μg/mL) and topical coagulants such as thrombin and tranexamic acid can be instilled during bronchoscopy. A small study has shown that tranexamic acid may be helpful when iced saline and topical epinephrine fail. For endobronchial lesions identified by bronchoscopy, modalities such as laser, photocoagulation, electrocautery, argon plasma coagulation, and cryotherapy are other options. Arterial embolization during angiogram can be very effective at controlling massive hemoptysis. In some instances, arterial embolization can be the definitive treatment for conditions such as bronchiectasis and arteriovenous

malformations. It also appears to be an appropriate option in patients who are deemed inoperable or are poor surgical candidates. Typically, arteriography is performed after the bleeding is localized by bronchoscopy. The limitations of arterial embolization depend on the experience of the provider, anatomic variance of the bronchial arterial tree, and inability to appreciate extravasation of contrast secondary to slow bleeding rates. If the cause of the hemoptysis is a chronic inflammatory condition such as bronchiectasis, any systemic artery in the thorax could potentially be the source of the bleeding. Should hemoptysis recur, repeat embolization can be performed safely. A potential complication of arterial embolization is accidental embolization of the anterior spinal artery, which originates from a bronchial artery in about 5% of the population.

Emergent surgery for massive hemoptysis is associated with a very high mortality rate and is typically used as a last resort. It is best to first stabilize the patient before proceeding with surgery. Surgery for massive hemoptysis after institution of control measures has mortality rates as low as 0% as opposed to 38% for emergent surgery. Surgical resection should be considered (1) when arterial embolization is unavailable or is deemed technically impossible; (2) when bleeding continues despite embolization; (3) when the volumes of expectorated blood or the cardiopulmonary sequelae of massive hemoptysis are so extreme as to be an imminent threat to survival; or (4) when the putative cause of massive hemoptysis is unlikely to be controlled by embolization, as in patients with suspected pulmonary artery perforation. Relative contraindications include poor underlying lung function, inoperable cancer, and active tuberculosis. Definitive treatment options for massive hemoptysis depend on the underlying cause. Lung cancer may be amenable to surgical resection or radiation therapy. Patients with massive hemoptysis resulting from infection may ultimately respond to antibiotic therapy. Patients with diffuse alveolar hemorrhage from disorders such as Goodpasture syndrome or systemic lupus erythematosus may respond to immunotherapy.

PNEUMOTHORAX

Pneumothorax is a relatively common disorder and is defined as air within the pleural space. It can be an incidental finding on a chest radiograph and cause few or no symptoms, or it can result in acute respiratory failure. The most common way air enters the pleural space is from the lung. However, air can also enter the pleural space through the chest wall because of penetrating trauma, by gas-producing organisms within the pleural space, or from air initiating in the

abdomen. A pneumothorax can occur because of underlying lung disease or trauma or can be iatrogenically induced. **Table 2** lists some common causes of pneumothorax.

Table 2. Common Causes of Pneumothorax

Primary Spontaneous (from subpleural blebs)
Associated With Underlying Lung Disease (Secondary)

- Chronic obstructive pulmonary disease
- Asthma
- Lung cancer
- Sarcoidosis
- Infections (pneumocystis, tuberculosis, necrotizing pneumonia)
- Endometriosis
- Cystic fibrosis
- Rheumatoid arthritis, Sjögren syndrome, ankylosing spondylitis
- Interstitial lung disease
- Genetic conditions (Marfan syndrome, Birt-Hogg-Dubé syndrome)
- Lymphangioleiomyomatosis
- Anorexia nervosa

Traumatic

- Penetrating chest trauma
- Blunt chest trauma
- Tracheal or bronchial rupture

Iatrogenic

- Transthoracic needle biopsy
- Subclavian central venous catheters
- Thoracentesis
- Transbronchial biopsy
- Lung resection
- Positive pressure ventilation
- Cardiopulmonary resuscitation

Information taken from Cremaschi P, Nascimbene C, Vitulo P, et al. Therapeutic embolization of bronchial artery: a successful treatment in 209 cases of relapse hemoptysis. *Angiology*. 1993;44:295-299 and Bintcliffe, OJ, et al. Spontaneous pneumothorax: time to rethink management? *The Lancet Respiratory Medicine*. 2015;3:578-588.

Spontaneous Pneumothorax

The term *spontaneous pneumothorax* refers to a pneumothorax of nontraumatic origin. It may be a primary spontaneous pneumothorax that occurs in otherwise

healthy individuals and is linked to the presence of subpleural blebs. A secondary spontaneous pneumothorax is linked to an underlying lung disease and is also described in **Table 2**. Smoking has been reported to increase the risk of primary spontaneous pneumothorax in up to 12% of healthy male smokers. Secondary atraumatic pneumothoraces carry a higher mortality than primary spontaneous pneumothoraces and may be more difficult to manage. One of the most common causes of secondary pneumothorax is chronic obstructive pulmonary disease.

Symptomatic primary or secondary spontaneous pneumothoraces require intervention. Secondary pneumothoraces are most likely to require intervention. Large-bore chest tubes are usually not required for management. Small-bore tubes of 14F or smaller are adequate. Smaller bore tubes are also better tolerated. Routine suction is usually not required. A persistent air leak after 2 to 4 days merits evaluation for thoracic surgery.

Traumatic Pneumothorax

Pneumothorax associated with blunt or penetrating chest trauma is common. In one published series, up to 26% of patients with blunt trauma sustained a pneumothorax and 76% of the pneumothoraces were occult. A pneumothorax seen on chest CT but not on chest radiograph is referred to as an *occult pneumothorax*. Frequently the patient has associated rib fractures. Blunt chest trauma can cause a pneumothorax by parenchymal injury with rib fracture, parenchymal injury from deceleration forces, alveolar rupture from crush forces, and alveolar rupture from increased intrathoracic pressure. A pneumothorax can develop without significant signs of external injury. Penetrating trauma involves direct injury to lung and the pleura. Occult pneumothoraces are commonly recognized with the use of chest CT scans and bedside ultrasonography. These pneumothoraces are typically very small and asymptomatic. Patients with occult pneumothorax who do not require positive pressure ventilation usually can be safely observed. Recommendations are mixed for the management of occult pneumothoraces in patients receiving positive pressure ventilation and include a conservative approach of observation or a more invasive approach involving placement of thoracostomy tubes. Patients with larger pneumothoraces may present with symptoms of pleuritic chest pain or dyspnea. On examination, patients may have tachypnea, hypoxia, or decreased or absent breath sounds on the side of the pneumothorax. The presence of subcutaneous emphysema in the neck or hemoptysis should raise concern for a traumatic injury to the trachea,

mainstem bronchus, or esophagus. Patients should be evaluated for evidence of displaced rib fractures and a flail chest. Absent breath sounds with the trachea deviated to the contralateral side should raise concerns for a tension pneumothorax.

Most patients with significant trauma undergo multiple body CT scans, which are very sensitive at diagnosing a pneumothorax. Upright chest radiographs are less sensitive and can miss up to 30% of pneumothoraces. Ultrasound has a higher reported sensitivity to detect a pneumothorax. A recent meta-analysis showed that ultrasound had 76% sensitivity for detecting pneumothoraces as opposed to 39.8% for chest radiograph. Placement of a chest tube is indicated if the patient is symptomatic or unstable, there is an associated hemothorax, the patient requires positive pressure ventilation, there is evidence of tracheobronchial rupture, or there is evidence of a tension pneumothorax. Tension pneumothorax should first be treated with immediate needle decompression followed by placement of the chest tube. A chest tube size of at least 32F has been recommended; however, smaller chest tubes may be considered. Up to 20% of traumatic pneumothoraces can have associated hemothoraces. There is some support in the literature for prophylactic doses of a first-generation cephalosporin for 24 hours to decrease the incidence of pneumonia or empyema in patients who require chest tubes for the management of a traumatic pneumothorax.

Iatrogenic Pneumothorax

An iatrogenic pneumothorax is not uncommon in the ICU. It is often due to a complication from placement of a central venous catheter, thoracentesis, transthoracic needle biopsy, cardiopulmonary resuscitation, or positive pressure ventilation. Pacemaker placement and bronchoscopy have been associated with pneumothorax but are uncommon causes. The incidence of pneumothorax complicating the placement of a subclavian venous catheter is about 1.5%, whereas the risk associated with transthoracic needle biopsy can be as high as 25%. Risk of pneumothorax is highest when the procedure is performed by less experienced providers. Most pneumothoraces that complicate procedures are small and are detected immediately after the procedure. However, some may develop up to 24 hours after the procedure. If the pneumothorax is small and the patient is asymptomatic and not receiving positive pressure ventilation, the patient can likely be treated with increased FIO_2 and observed. Placing the patient on humidified 100% oxygen potentially increases the rate of reabsorption 4

times faster compared with room air. Serial chest radiographs are needed to ensure that the pneumothorax is not expanding. Expansion suggests an ongoing air leak from the lung, and in such cases a chest tube should be placed. Needle aspiration remains an option for select iatrogenic and noniatrogenic pneumothoraces. Asymptomatic patients with a larger pneumothorax (>20% on chest radiograph) or presenting with symptoms such as dyspnea post procedure may benefit from needle aspiration. This is performed by inserting a 16- or 18-gauge catheter over a needle into the pleural space at the level of the second intercostal space in the midclavicular line. Air is aspirated through the catheter with a syringe once the needle is removed. This is best accomplished by using a 3-way stopcock and a 50- to 60 mL-syringe. Ultrasound may facilitate pneumothorax location and limit complications. Needle aspiration has been associated with a resolution rate as high 90%. If more than 2.5 L of air is removed without the development of resistance to withdrawal, this suggests the presence of a persistent air leak. Some literature suggests that the aspiration of air greater than 550 mL predicts the need for chest thoracostomy. The catheter is typically removed when resistance is detected with aspiration. Postprocedure serial chest radiographs should be performed. Increasing pneumothorax suggests the presence of an air leak and requires placement of a chest tube. A meta-analysis comparing needle aspiration versus chest tube in the management of spontaneous pneumothoraces showed no difference in outcome but a decreased hospital length of stay when aspiration was used. Needle aspiration has been used successfully for small iatrogenic pneumothoraces. For patients with persistent air leaks, patients receiving positive pressure ventilation, or those with signs of hypoxia, respiratory distress, or respiratory failure, a chest tube should be placed.

Pneumothorax From Positive Pressure Ventilation

Pneumothorax is one of several manifestations of pulmonary barotrauma from positive pressure ventilation and can result in severe hypoxia, hypotension, and even cardiac arrest due to the development of a tension pneumothorax. Other repercussions of barotrauma include pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, and gas embolism. The risk of pneumothorax with positive pressure ventilation has been estimated to range from 3% to 10%. Risk factors for developing a pneumothorax with positive pressure ventilation include chronic obstructive pulmonary disease, asthma, chronic interstitial lung disease, right mainstem intubation, and acute respiratory distress syndrome (ARDS). Patients receiving high-frequency oscillatory ventilation appear to be at a much

higher risk for developing pulmonary barotrauma, with an incidence as high as 26%.

The appearance of signs such as sudden tachycardia, worsening hypoxia, tachypnea, and/or subcutaneous emphysema may suggest the presence of a pneumothorax. If the patient develops sudden hypotension with evidence of tracheal deviation, a tension pneumothorax should be suspected. A sudden increase in both peak and plateau airway pressures should also raise the concern for a pneumothorax. Other findings that suggest a pneumothorax include pulsus paradoxus on arterial line tracings, decreased ipsilateral breath sounds, or hyperresonance on percussion. The challenge in care is that clinical findings in a ventilated patient can be highly unreliable. In one case series review, mechanically ventilated patients with tension pneumothorax rarely exhibited jugular venous distention or tracheal deviation. Primary findings were an increase oxygen requirement and hypotension. Detection of a pneumothorax in a mechanically vented patient often requires vigilance, clinical suspicion, and frequent reevaluation.

A chest radiograph and/or ultrasound study should be performed immediately if a pneumothorax is suspected. However, if the patient is unstable and evidence suggests a tension pneumothorax (absent breath sounds, contralateral tracheal deviation, and hypotension), needle decompression should be performed immediately without waiting for diagnostic studies. The chest radiograph should be performed with the patient sitting upright if possible. A better option than a chest radiograph is a bedside ultrasound. Bedside ultrasound has a documented superior sensitivity to chest radiograph for occult pneumothorax detection. The bedside ultrasound offers the advantage of immediate point of care access. In trained hands, bedside ultrasound has been shown to diagnose 92% of occult pneumothoraces found on chest CT. If chest radiography or ultrasonography is inconclusive, chest CT should be considered.

Efforts should be made to prevent the development of barotrauma in patients receiving positive pressure ventilation. The best approach appears to be keeping plateau airway pressures below 30 cm H_2O. Elevated peak airway pressures do not predict the risk of barotrauma, and barotrauma appears unlikely to develop at peak airway pressures less than 50 cm H_2O.

INHALATIONAL INJURIES

Inhalational injuries can be divided into 3 categories: thermal injuries to the

airways, chemical inhalational injuries to the airways and lung, and systemic effects of inhaled toxins.

Thermal Injury

Inhalational injury is the leading cause of death in burn patients. Patients with cutaneous burns have an increased mortality if they have associated inhalational injuries. Two-thirds of all patients with burns on more than 70% total body surface area are at high risk for inhalational injuries. In addition, patients are at risk for the effects of smoke inhalation. This section addresses thermal injuries to the airway, whereas systemic effects are discussed later.

Thermal burns are typically limited to the upper airway, specifically the supraglottic airway. This is mostly due to the effective heat exchange properties of the upper airway, which is very efficient at decreasing the temperature of air before it reaches the lower airway. Exceptions to this are thermal injuries due to inhalation of steam and inhalation of superheated gases, because the upper airway cannot effectively cool steam.

Patients with thermal injuries to the airway can develop upper airway edema rapidly, thus risking oxygenation and compromising the patency of the airway. In addition, fluid resuscitation needed in patients with skin burns can potentially worsen upper airway edema. A burn patient with inhalational injuries may require as much as 50% more fluids during the first 24 hours compared with a burn patient without inhalational injury. About one-third of hospitalized patients with thermal injuries will develop acute airway obstruction. Predicting who will develop significant airway compromise is difficult. Signs and symptoms that suggest significant inhalational injury and thus the potential need for intubation include cough (especially if it produces carbonaceous material), hoarseness, wheezing, stridor, deep facial and neck burns, singed nasal hairs, altered mental status, blistering or edema of the oropharynx, and the presence of hypoxia or hypercapnia.

In addition to undergoing routine studies such as a chest radiograph and arterial blood gas, patients with any of these signs or symptoms should undergo a fiberoptic bronchoscopy or laryngoscopy to look for evidence of mucosal injury. Initial findings suggesting airway injury include edema, erythema, ulceration, or soot throughout the tracheobronchial tree. Within several days, subacute changes occur to the airway mucosa and include necrosis and hemorrhage. A normal initial examination does not rule out significant upper airway injury, and there is

no accepted method for grading thermal injuries to the airway. Upper airway edema can continue to progress at various speeds during the first 18 to 24 hours. Patients believed to be at high risk for upper airway thermal injuries might require repeated bronchoscopy or laryngoscopy during the first 24 hours to look for evidence of progressing edema and pending airway compromise. Another approach is to prophylactically intubate patients believed to be at very high risk for potential upper airway compromise. Because patients with thermal injuries to their upper airway typically develop thick secretions, a larger oropharyngeal tube should be used to aid in suctioning and to minimize the risk of tube obstruction. In addition, the endotracheal tube should be well secured to prevent accidental extubation or self-extubation. Edema typically resolves in 3 to 5 days. Treatment is supportive. Systemic corticosteroids do not decrease upper airway edema. Survivors with thermal injuries to the airways risk formation of granulation tissue and airway stenosis.

Chemical Inhalational Injuries

A number of chemicals have been identified as agents that can cause serious injury to the upper and lower airways and to the lung itself. Some of these agents are listed in **Table 3**. Chemical inhalational injuries frequently present with nonspecific symptoms, which sometimes makes the diagnosis difficult in the absence of an obvious history of exposure. In general, the less water-soluble the chemical is, the more likely it is to reach the lower airways. In addition, exposure time (whether the patient can minimize exposure by breath holding) and minute ventilation affect the extent of the exposure.

Table 3. Partial List of Common Chemical Inhalants

More water soluble • Chlorine • Ammonia • Sulfur dioxide • Hydrogen chloride • Hydrogen fluoride
Less water soluble • Nitrogen dioxide • Phosgene • Ozone • Formaldehyde • Toluene

Water-soluble chemicals tend to dissolve and concentrate in the mucous in the upper airway, where they can then be absorbed into the blood, posing a risk for additional systemic toxicity. Less water-soluble chemicals typically do not dissolve until they are well into the lower respiratory tract and are less likely to produce early symptoms. Mucosal injuries to the nasopharynx and larynx are seen early with inhalational injuries. Symptoms include hoarseness, stridor, and laryngeal edema. Patients with upper airway symptoms from inhalation of water-soluble gases typically have irritation to their eyes, nose, and throat. Symptoms may be minimal within the first several hours after exposure, despite evidence on laryngoscopy or bronchoscopy of mucosal edema. Within 6 to 8 hours after exposure, mucosal ulceration, hemorrhage, and worsening edema of the upper airway can be seen. Injury to the trachea and lower airway also can be noted, consisting of airway edema, mucopurulent pseudomembranes, and bronchorrhea. The chemical irritant can result in impaired mucociliary clearance and the development of atelectasis, tracheobronchitis, or pneumonia. Extensive mucosal sloughing is evident 48 to 72 hours after exposure. With exposures to high concentrations of very water-insoluble chemicals, ARDS can develop. Although ARDS can be seen within hours after very high exposures, it is more likely to be seen 24 to 48 hours after exposure.

In addition to causing hoarseness and stridor, chemical inhalational injuries can result in productive cough, hemoptysis, and wheezing. Cough is typically the first symptom the patient experiences. Progressive dyspnea should raise concern for the development of pulmonary edema, atelectasis, or pneumonia. Patients with chemical inhalational injuries can develop rapid and unpredictable life-threatening upper airway obstruction. Therefore, patients should undergo serial fiberoptic airway examination to evaluate the progression of the upper airway edema during the first 24 to 48 hours post exposure. If this is not possible, clinicians should consider prophylactic intubation. Progressive upper airway edema on examination should prompt consideration for intubation.

The patient's oxygenation should be assessed with arterial blood gas studies. Patients should undergo serial chest radiographs to reveal any evidence of atelectasis, pneumonia, or pulmonary edema, especially in patients with any degree of hypoxemia. Treatment is mostly supportive. Supplemental oxygen should be administered. Few treatments or antidotes are available for most chemical inhalants (carbon monoxide and cyanide exposures are discussed in the following section). An inhaled β-agonist may be helpful in reversing some

bronchoconstriction and may aid in pulmonary toilet by increasing mucociliary clearance and inducing a more productive cough. Patients with chlorine gas exposure may benefit from treatment with inhaled budesonide in addition to an inhaled β-agonist. Nebulized solutions of 3.75% or 4.2% sodium bicarbonate have been proposed in the treatment of chlorine gas exposure, but their effectiveness has not been studied. For patients exposed to phosgene, treatment with *N*-acetylcysteine, ibuprofen, aminophylline, isoproterenol, and colchicine might be of benefit. Systemic corticosteroids are considered contraindicated as they do not lessen the degree of airway edema and may increase the risk for superimposed pneumonia.

Patients who survive chemical inhalational injuries are at risk of developing reactive airway dysfunction syndrome, constrictive bronchiolitis (bronchiolitis obliterans), or pulmonary fibrosis.

Systemic Effects of Inhaled Toxins

The most commonly encountered inhaled toxin is carbon monoxide (CO). Others include cyanide, nerve gases such as sarin, and insecticides. These chemicals can cause severe injury attributable to their toxic effects. Other gases such as nitrogen, helium, methane, propane, and natural gas can cause simple asphyxiation by displacing oxygen and decreasing the patient's F_{IO_2}. If the concentration of the gas results in an F_{IO_2} less than 0.16, patients are at risk of developing impaired judgment, altered mental status, and death.

Carbon Monoxide

CO poisoning is one of the most common types of poisoning. Most unintentional poisonings with CO occur in the winter months due to the production of CO from poorly functioning heating units or burning of fossil fuels for heating. CO poisoning is also seen in patients who experience smoke inhalation from fires. CO rapidly diffuses across the alveolar membrane and binds to hemoglobin with a more than 240-fold greater affinity than oxygen. The resulting carboxyhemoglobin (COHb) starves cells of oxygen by several mechanisms. COHb shifts the oxygen dissociation curve to the left, which in turn decreases unloading of oxygen at the tissue level. As CO levels in cells increase, CO binds to cytochrome oxidase in the electron transport chain, resulting in uncoupling of mitochondrial oxidative phosphorylation and impairment of adenosine triphosphate production.

Symptoms of CO poisoning are highly variable and nonspecific and include malaise, nausea, vomiting, dyspnea, headache, dizziness, and confusion. With higher levels of CO poisoning, symptoms of angina, heart failure, seizures, coma, and death can occur. Physical examination is typically not helpful as there are no specific signs suggesting CO poisoning. The diagnosis of CO poisoning can be made based on history of potential exposure coupled with an elevated COHb level. A potential clue to CO poisoning is a discrepancy between the arterial oxygen saturation as measured on a pulse oximeter (Spo_2) and the arterial oxygen saturation (Sao_2) as measured on arterial blood gas studies. Currently available pulse oximeters are unable to distinguish between oxygenated hemoglobin (Hbo_2) and COHb, resulting in a spuriously high Spo_2 reading. COHb can be detected using co-oximetry. COHb levels above 15% are consistent with CO poisoning and warrant treatment. All patients should undergo electrocardiography and measurement of cardiac enzymes to evaluate for cardiac ischemia or infarction.

Treatment for CO poisoning is 100% oxygen, which displaces CO from hemoglobin. Treatment is based on COHb levels. Oxygen should be administered immediately. One hundred percent oxygen at 1 atmosphere (atm) reduces the half-life of COHb to 60 to 90 minutes compared with 4 to 6 hours with room air. When 100% oxygen is used at 3 atm (hyperbaric), the half-life decreases to 20 to 30 minutes. Recommendations for the use of hyperbaric oxygen in CO poisoning are listed in **Table 4**. Even with quick and appropriate treatment, a significant number of survivors of CO poisoning suffer some degree of neurological impairment.

Table 4. Recommendations for Using Hyperbaric Oxygen for Carbon Monoxide Poisoning

- Carboxyhemoglobin level >25 %
- Severe neurological symptoms or loss of consciousness
- Electrocardiographic evidence of acute myocardial infarction or ischemia
- Dysrhythmias
- Carboxyhemoglobin level >20% in pregnant patients
- Failure to improve after 4 hours of treatment with 100% oxygen at 1 atm

Information taken from Miller K, Chang A. Acute inhalational injury. *Emerg Med Clin N Am*. 2003;21:533-557.

Cyanide

Inhalational poisoning from cyanide occurs most commonly in victims of fires,

especially when items such as plastics, insulation, upholstery, and synthetic rubber are consumed in the fire. Cyanide gas can be released in industrial accidents involving metal extraction in mining, plastic and rubber manufacturing, and jewelry electroplating. Hydrogen cyanide can be released when cyanide salts are mixed with acid.

Cyanide rapidly binds to mitochondrial cytochrome oxidase, blocking oxidative phosphorylation and the production of adenosine triphosphate. Cells then switch to anaerobic metabolism, resulting in the production of lactic acid. Despite adequate levels of oxygen, cells are unable to use oxygen in the production of adenosine triphosphate.

Signs and symptoms of cyanide poisoning include altered mental status, tachypnea, tachycardia, flushing, seizures, hypotension, and lactic acidosis. Patients typically have adequate PaO_2 levels. The diagnosis of cyanide poisoning should be entertained in all patients with the appropriate history of potential exposure coupled with significant lactic acidosis in the setting of adequate oxygenation. Lactate levels greater than 10 mmol/L are common. High venous PO_2 levels suggest the possibility of cyanide poisoning.

The diagnosis can be confirmed by measuring blood cyanide levels. Levels correlate with symptoms; levels of 0.5 to 1 mg/L correlate with tachycardia and flushing, levels of 1 to 2.5 mg/L correlate with altered mental status, levels of 2.5 to 3 mg/L correlate with coma, and levels greater than 3 mg/L correlate with death.

Initial treatment includes basic resuscitation with intubation, oxygenation, and blood pressure support with fluids and vasopressors. Mouth-to-mouth resuscitation is considered contraindicated in patients with cyanide poisoning given the potential for cyanide exposure to the rescuer. All patients with cyanide poisoning should undergo appropriate decontamination of skin with soap and water, and rescue personnel should wear protective clothing and respirators until the patient is fully decontaminated.

Antidotes are available for cyanide poisoning, including include sodium nitrite, amyl nitrate, sodium thiosulfate, and hydroxocobalamin. Sodium nitrite and amyl nitrate work by causing the oxidation of iron in hemoglobin, producing methemoglobinemia. Cyanide then binds to methemoglobin instead of mitochondrial cytochrome oxidase. Sodium nitrite is much more effective at producing methemoglobinemia than is amyl nitrate and is preferred. Doses of 10

mg/kg sodium nitrite are given IV. The use of either sodium nitrite and amyl nitrate is contraindicated in patients with concurrent CO poisoning.

Sodium thiosulfate works as an antidote to cyanide poisoning by donating sulfur groups to the enzyme rhodanese, which in turn transforms cyanide into thiocyanate, a less toxic chemical. Thiocyanate is excreted in the urine, so patients with abnormal renal function who receive sodium thiosulfate may require hemodialysis to assist in its removal. A typical dose of sodium thiosulfate is 1.65 mL/kg of 25% solution IV.

Hydroxocobalamin has a higher affinity for intracellular cyanide than mitochondrial cytochrome oxidase. Binding of cyanide by hydroxocobalamin results in the formation of cyanocobalamin (vitamin B_{12}), which is excreted in the urine. A typical dose of hydroxocobalamin is 70 mg/kg. It is probably best to treat patients with cyanide poisoning with more than 1 antidote. Studies suggest that using sodium thiosulfate and hydroxocobalamin concurrently is the most effective and safest therapy for cyanide poisoning.

Organophosphates

As with cyanide poisoning, organophosphate poisoning can occur from inhalation, ingestion, and absorption through the skin. Most organophosphate poisoning occurs as a result of exposure to agricultural insecticides. Organophosphate poisoning can also occur from exposure to chemical warfare agents, specifically tabun, sarin, and soman.

Organophosphates bind to acetylcholinesterase, which results in ongoing stimulation of the acetylcholine receptor at the motor endplate. Common acute signs and symptoms of organophosphate poisoning include miosis, excess lacrimation and salivation, bronchospasm, urination, vomiting, diarrhea, bradycardia, heart block and prolonged QTc, muscle fasciculations, muscle weakness, and paralysis. Most fatalities are due to respiratory failure resulting from direct central nervous system respiratory depression and respiratory muscle failure.

Diagnosis is typically a clinical diagnosis with the appropriate history of exposure. The diagnosis is suggested by rapid but transient improvement after the administration of 1 mg of atropine. Initial treatment should include basic resuscitation and decontamination of the patient. Patients with altered mental status should be intubated. Patients can rapidly develop respiratory failure.

Succinylcholine should not be used in patients with organophosphate poisoning; succinylcholine is metabolized by plasma cholinesterase (also inhibited by organophosphates), so patients can have prolonged paralysis with this agent.

Atropine should be administered at doses of 2 to 5 mg IV, and the dose can be repeated every 3 to 5 minutes as needed. Atropine competitively binds to muscarinic receptors, but not nicotinic receptors. Neuromuscular dysfunction suggesting nicotinic receptor involvement should be treated with concurrent pralidoxime. Pralidoxime should be administered at a loading dose of 30 mg/kg IV, followed by a continuous infusion of 8 mg/kg/h. Pralidoxime should not be given without atropine due to known initial acetylcholinesterase inhibition and worsening symptoms associated with onset of action. The initial dose should be given over 30 minutes to prevent cardiac arrest. Diazepam has been used to treat seizures; no evidence is available to show that phenytoin is effective. Two studies suggested that prophylactic use of diazepam may decrease neurological and cognitive dysfunction in survivors of organophosphate poisoning.

Smoke Inhalation

Smoke inhalation deserves special mention because survivors of fires often sustain a combination of thermal injury to their airway, asphyxiation, and the potential for CO and cyanide poisoning. Other chemicals released during combustion include chlorine, phosgene, sulfur dioxide, nitrogen dioxide, and nitric oxide, which can result in significant chemical injury. Clinicians who treat victims of smoke inhalation must be aware of all the potential injuries discussed in this chapter.

SUMMARY

Massive hemoptysis, pneumothorax, and inhalational injuries are common, life-threatening conditions encountered by intensivists and present unique diagnostic and management challenges. Intensivists must to be prepared to manage these conditions.

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CHAPTER 24

Immunological Lung Disease

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Key words: diffuse alveolar hemorrhage, immunological lung disease, vasculitis

Immunological lung disease is a relatively common cause of respiratory dysfunction that can require critical care management and may be life threatening. Common clinical pulmonary manifestations include hypoxemia, hemoptysis, and respiratory failure. The clinical disorders that may give rise to immunological lung disease are varied and include connective tissue diseases, pulmonary vasculitides, circulating antibodies, and complications after transplant. Often, the major challenge facing the intensivist is determining whether the clinical presentation is a result of an infection or the inflammatory process that comprises immunological lung disease. Optimal treatment depends on establishing the cause of the disorder and making a timely diagnosis. This chapter reviews several connective tissue disorders and their pulmonary manifestations, systemic capillary leak syndrome, posttransplant respiratory disorders, and diffuse alveolar hemorrhage.

CONNECTIVE TISSUE DISEASES AND THE LUNG

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an immunologically mediated autoimmune disorder that is characterized by multisystem involvement and typically targets women of childbearing age. Women are affected 6 to 10 times more often than men, and the disorder is more common in the Hispanic and African American populations. Pulmonary involvement can take a variety of forms (**Table 1**) and is more common in males, particularly when the disease is drug induced.

Table 1. Pulmonary Involvement in Systemic Lupus Erythematosus

Pleural disease
Pleural effusion
Pleuritis
Interstitial lung disease
Nonspecific interstitial pneumonia
Lymphocytic interstitial pneumonia
Usual interstitial pneumonia
Bronchiectasis
Acute lupus pneumonitis and/or acute respiratory distress syndrome
Diffuse alveolar hemorrhage
Pulmonary hypertension
Thrombotic lung disease
Pulmonary embolus
Pulmonary infarction
Pulmonary microthrombosis
Postpartum hemolytic uremic syndrome
Shrinking lung disease secondary to diaphragmatic dysfunction or weakness
Obstructive lung disease
Upper airway disease
Infection
Community-acquired pathogens
Opportunistic pulmonary infection
Drug-induced lung disease
Cyclophosphamide
Methotrexate

Pleural disease, including pleuritis and pleural effusion, is the most common pulmonary manifestation of SLE and is found in up to 50% of patients with SLE. The pleural effusions tend to be small, bilateral, and exudative. Low glucose and complement levels are typical. Long-term effusions may result in a “trapped lung,” but lupus pleural effusions typically improve with either nonsteroidal anti-inflammatory agents or low-dose corticosteroid treatment.

Acute lupus pneumonitis is found in 1% to 12% of SLE patients. Patients present with fever, cough, pleuritic chest pain, dyspnea, hypoxemia, hemoptysis, and crackles on physical examination. Predominantly lower lobe pulmonary infiltrates and pleural effusions are noted on chest radiograph, with ground glass opacities and/or honeycombing seen on chest computed tomography (CT) scan. The clinical picture suggests possible infection, and clinicians should provide initial antibiotic coverage and pursue further evaluation to identify the presence or absence of pulmonary infection. Bronchoscopy with bronchoalveolar lavage (BAL) is typically used to obtain lower respiratory tract samples to diagnose infection and/or the presence of diffuse alveolar hemorrhage (DAH). Treatment of acute lupus pneumonitis typically involves the use of moderately high-dose

corticosteroids (1.0-1.5 mg/kg prednisone or equivalent) but can involve pulse-dose steroids for patients with severe hypoxemia and marked pulmonary infiltrates.

Interstitial lung disease in patients with SLE usually develops insidiously and is manifest as a nonproductive cough and progressive dyspnea on exertion. Chest auscultation demonstrates bibasilar end-inspiratory crackles. High-resolution chest CT will demonstrate the typical pattern of interstitial disease involvement such as nonspecific interstitial pneumonia, usual interstitial pneumonia, or lymphocytic interstitial pneumonia. Pulmonary function testing demonstrates restrictive changes and a reduced diffusion capacity for carbon monoxide. Corticosteroids with or without cyclophosphamide, azathioprine, or mycophenolate are the typical treatment strategy.

A group of patients with SLE have dyspnea and small lung volumes with elevated hemidiaphragms on chest radiograph. Pulmonary function testing will show restrictive lung disease with decreased maximum inspiratory and expiratory pressures. This condition is termed *shrinking lung syndrome* and is related to diaphragmatic weakness, possibly from an inflammatory myopathy or phrenic nerve neuropathy. The condition is treated with corticosteroids with or without other immunosuppressive agents. The immunosuppressive agents that have been used effectively in the management of shrinking lung syndrome include azathioprine, methotrexate, cyclophosphamide, and rituximab.

Patients with SLE may develop a rare but life-threatening complication, DAH, which is manifest as cough, dyspnea, and pulmonary infiltrates with anemia. Many patients have hemoptysis and hemosiderin-laden macrophages in the sputum or lavage fluid; however, in one-third of cases, hemoptysis is not present. The diagnosis is made by characteristic findings on bronchoscopy with BAL (please see later discussion).

Pulmonary hypertension is not as common in SLE as it is in scleroderma and mixed connective tissue disease. Lupus patients with pulmonary hypertension more commonly have Raynaud phenomenon, and histologically the muscular arteries will demonstrate narrowing from fibrocollagenous intimal thickening, medial hypertrophy, and alterations in the elastic lamina. Clinical and functional improvement has been seen with cyclophosphamide with or without corticosteroid treatment. When immunosuppressive therapy does not lead to improvement, pulmonary hypertension is typically managed with phosphodiesterase 5 inhibitors, antiendothelin agents, and prostaglandin analogs

in similar fashion to other causes of pulmonary hypertension. Lupus patients with antiphospholipid disease are potentially susceptible to pulmonary embolism, pulmonary infarction, pulmonary hypertension, pulmonary arterial thrombosis, pulmonary microthrombosis, acute respiratory distress syndrome (ARDS), intra-alveolar pulmonary hemorrhage, and postpartum hemolytic uremic syndrome. Up to 30% of SLE patients can have disorders of the upper airway. The upper airway involvement can include laryngeal mucosal inflammation, mucosal ulcerations, cricoarytenoiditis, vocal cord paralysis, vocal cord edema, and airway obstruction from necrotizing vasculitis. Bronchial wall edema with bronchiolitis and/or bronchiectasis can be found on high-resolution chest CT scan. These conditions are typically treated with prednisone.

Rheumatoid Arthritis

The systemic manifestations of rheumatoid arthritis can take a variety of forms when the pulmonary system is involved (**Table 2**). Rheumatoid pleural disease is characteristically an exudative pleural effusion with an elevated lactate dehydrogenase level and a very low glucose level. The pleural fluid may even appear milky and resemble a chylous effusion, but when chemical testing reveals an elevated cholesterol level rather than the presence of chylomicrons or an increased triglyceride level, the pleural fluid meets the definition of a pseudochylous effusion. Cytological examination of the pleural fluid may demonstrate elongated multinucleated macrophages or round multinucleated macrophages.

Table 2. Pulmonary Involvement in Rheumatoid Arthritis

Pleuritis
Vasculitis
Interstitial lung disease
Bronchiolitis obliterans
Organizing pneumonia or bronchiolitis obliterans organizing pneumonia
Bronchiectasis
Pulmonary nodules
Rheumatoid pneumoconiosis (Caplan syndrome)
Upper airway obstruction (cricoarytenoid cartilage abnormalities)
Drug toxicity (methotrexate, gold penicillamine)
Opportunistic infection

Patients with rheumatoid arthritis may demonstrate evidence of vasculitis or interstitial lung disease. The most common forms of interstitial lung disease in rheumatoid arthritis are nonspecific interstitial pneumonia and usual interstitial

pneumonia. Airflow obstruction can suggest the presence of bronchiolitis obliterans or bronchiectasis. Both can be further evaluated with high-resolution chest CT scans. Chest imaging may demonstrate patchy areas of organizing pneumonia which, on biopsy, demonstrate bronchiolitis obliterans–organizing pneumonia, which is now simply called *organizing pneumonia*. This condition is typically responsive to corticosteroids but can recur if the steroids are tapered too rapidly. The chest CT may demonstrate pulmonary nodules (rheumatoid nodules) that can predate the presence of subcutaneous nodules. The challenge is to differentiate these benign nodules from infection or neoplasm. In the setting of occupational exposure, nodules may represent rheumatoid pneumoconiosis, and in coal mining the condition is termed *Caplan syndrome*. Upper airway obstruction from fusion of the cricoarytenoid cartilage has been described and can produce clinical symptoms and abnormalities on flow-volume loop testing.

Patients with rheumatoid arthritis are commonly treated with medications that may have potential pulmonary toxicity or lead to immunosuppression that sets the stage for opportunistic infection. When infection is suspected, the clinician should obtain appropriate material for culture and sensitivity testing and should begin empirical broad-spectrum antibiotic therapy and treatment for opportunistic pathogens until the laboratory results are available. Anti–tumor necrosis factor (TNF) therapy has been associated with reactivation of old tuberculosis and a predisposition to fungal infections. Methotrexate is one of the most common causes of drug-induced lung disease in patients with rheumatoid arthritis and is associated with pulmonary infiltrates that may have an acute, subacute, or chronic presentation. Patients with methotrexate pneumonitis, which appears to be a hypersensitivity process, improve when the methotrexate is discontinued. Steroids are typically administered to help with resolution.

Scleroderma (Systemic Sclerosis) and the Respiratory System

Pulmonary involvement is the second most common visceral complication in systemic sclerosis (SSc) and is found in more than 70% of patients. The median survival of patients with pulmonary involvement is 78 months. SSc is manifested by deposits of excess collagen and extracellular matrix in the skin and other organs. Microvascular abnormalities are found, and autoantibodies against the centromere, topoisomerase 1, and RNA polymerase I and III are common. The pulmonary involvement in SSc can take a variety of forms (**Table 3**), including interstitial lung disease, pulmonary vascular disease with or without pulmonary hypertension, pleural disease, aspiration, bronchiectasis, spontaneous

pneumothorax, drug-induced lung disease, and neoplastic disease.

Table 3. Pulmonary Involvement in Systemic Sclerosis

Interstitial lung disease
Nonspecific interstitial pneumonia
Usual interstitial pneumonia
Diffuse alveolar damage
Cryptogenic organizing pneumonia
Pulmonary vascular disease with or without pulmonary hypertension
Pleural disease
Aspiration injury
Bronchiectasis
Small airways disease
Respiratory muscle weakness
Spontaneous pneumothorax
Drug-induced lung disease
Pneumoconiosis (silicosis)
Neoplasm

Patients with SSc interstitial lung disease typically report dyspnea on exertion and nonproductive cough. They may also report malaise and atypical chest pain. Lung auscultation typically reveals dry, "Velcro-like" inspiratory crackles, and patients may have the skin changes and digits typically seen with SSc. With more severe disease or pulmonary hypertension, clinicians may note changes of cor pulmonale with evidence of a loud pulmonic component of the second heart sound (P_2), right ventricular heave, right-sided (tricuspid) regurgitant murmur, hepatojugular reflux, pitting peripheral edema, and peripheral cyanosis. Pulmonary function abnormalities are characterized by restrictive lung disease with a decrease in total lung capacity, functional residual capacity, and forced vital capacity; the diffusion capacity for carbon monoxide is decreased as well. Various radiographic abnormalities may be seen. Typical high-resolution chest CT demonstrates symmetrical basal reticulonodular changes, narrow subpleural crescent in the posterior segment of the lower lobes, honeycombing with large cystic air spaces, and areas of alveolitis with ground glass opacity. Lower lung zones are more commonly involved compared with upper lung fields. Chest CT may demonstrate areas of ground glass opacity as in nonspecific interstitial pneumonia or may show interstitial thickening with traction bronchiectasis and honeycomb cysts as in usual interstitial pneumonia. BAL in patients with SSc lung disease reveals lymphocytes, eosinophils, and polymorphonuclear leukocytes, and increased endothelin is seen in patients with pulmonary hypertension. In patients with idiopathic pulmonary fibrosis, the levels of interleukin 1 and interleukin 1 receptor agonist in the lavage fluid are increased.

Those with ground glass infiltrates and evidence of alveolitis will manifest decreased lung function on pulmonary function testing. The interstitial lung disease of SSc may be associated with several biomarkers, such as surfactant protein D, Krebs von den Lungen-6 glycoprotein, soluble E selectin, chemokine ligand 13, exhaled nitric oxide, polymorphonuclear elastase, and von Willebrand factor.

Treatment of SSc lung disease has targeted the use of various immune-suppressing regimens including cyclophosphamide, penicillamine, corticosteroids, plasmapheresis, mycophenolate mofetil, interferon, pirfenidone, anti-AGF-B antibodies (gene that encodes minor fimbrial subunit of Tafi or thin aggregate fimbriae), imatinib mesylate, dasatinib, nilotinib, and rituximab. Lung transplant is a potential option for management of severe pulmonary involvement with SSc.

Approximately 8% to 12% of patients with SSc will manifest pulmonary arterial hypertension (PAH), which can be detected by echocardiography as a screening method to evaluate estimated peak pulmonary artery systolic pressures. The pulmonary vascular lesion of patients with SSc-associated pulmonary hypertension resembles that of idiopathic pulmonary hypertension. Patients with SSc-PAH should undergo formal evaluation with right-sided heart catheterization and vasoreactivity testing as well as testing with functional assessments, such as the 6-minute walk test. The management of patients with SSc-PAH is complex and beyond the scope of this chapter. These individuals should be managed by an expert in pulmonary hypertension, and their management strategy will typically involve the use of phosphodiesterase 5 inhibitors, endothelin antagonists, and prostanoids, alone or in combination.

Mixed Connective Tissue Disease

Mixed connective tissue disease is a clinical entity that combines clinical features of multiple autoimmune diseases, such as SSc, SLE, polymyositis, and Sjögren syndrome. The pulmonary manifestations of mixed connective tissue disease can include interstitial lung disease and pulmonary fibrosis, pleural disease, alveolar hemorrhage, aspiration pneumonitis, pulmonary hypertension, pulmonary vasculitis, pulmonary embolism, obstructive airways disease, diaphragmatic dysfunction, and pulmonary infections. Interstitial lung disease and pulmonary fibrosis are the most common pulmonary manifestations of mixed connective tissue disease. Patients are typically treated with corticosteroids with or without additional immune suppressants.

Granulomatosis With Polyangiitis (Formerly Wegener Granulomatosis)

Granulomatosis with polyangiitis (GPA) is the most common of the anti–neutrophil cytoplasmic antibody (ANCA)–associated vasculitides. It is typically manifested by involvement of the upper and lower respiratory tract and the kidneys. Limited GPA reflects only upper and lower respiratory tract involvement and appears to spare the kidneys. GPA is characterized by necrotizing granulomatous vasculitis of the small blood vessels of the lungs and other organs and focal necrotizing glomerulitis. The disorder can be a life-threatening illness, particularly when patients present with respiratory failure, airflow obstruction, alveolar hemorrhage, or renal failure. Common clinical manifestations include epistaxis, sinusitis, rhinorrhea, otitis, hearing impairment, otalgia, nasal mucosal ulcerations, bone and cartilage deformities of the upper airway, cough, hemoptysis, chest pain, endobronchial lesions, subglottic or bronchial stenosis, and glomerulonephritis. Less common clinical manifestations include arthralgia, myalgia, arthritis, purpura, cutaneous ulcers, vesicles, skin nodules, orbital pseudotumors, conjunctivitis, uveitis, episcleritis, scleritis, proptosis, fever, weight loss, malaise, peripheral or central neuropathy, headache, and coronary vasculitides. The diagnostic criteria for GPA include nasal or oral inflammation, abnormal chest radiograph, abnormal urinary sediment, and the presence of granulomatous vasculitis on biopsy. If no biopsy is available, the presence of hemoptysis can be used as a fourth component for diagnosis. The radiographic manifestations can be unilateral or bilateral and commonly include infiltrates and/or nodules. The nodules may demonstrate cavitation. A wide range of radiographic findings may be present, including pleural effusions and lymphadenopathy. Patients typically manifest a normochromic, normocytic anemia, with mild thrombocytosis and leukocytosis. The erythrocyte sedimentation rate typically is elevated, and there are increased levels of circulating immunoglobulin (Ig) G and IgA, as well as other immune complexes, such as rheumatoid factor. With renal involvement, evidence of hematuria, proteinuria, and red blood cell casts is found. The detection of cytoplasmic–antineutrophil cytoplasmic antibody (c-ANCA) is highly specific and sensitive for the diagnosis of GPA, and c-ANCA present in more than 90% of patients. Treatment with corticosteroids and cyclophosphamide typically results in significant improvement and, in a majority of cases, complete remission. Rarely, plasmapheresis may be required.

Goodpasture Syndrome

Goodpasture syndrome is an uncommon disorder that is also known as anti–glomerular basement membrane (GBM) antibody disease. Anti-GBM antibody disease is typically an acute or rapidly progressive form of crescentic glomerulonephritis that is associated with pulmonary hemorrhage in 30% to 40% of patients. The anti-GBM antibodies are usually IgG type 1 or 3 and are deposited linearly along glomerular capillaries and occasionally in the distal tubules. The target antigen for the anti-GBM antibody is the α3 chain of type IV collagen. The risk for anti-GBM antibody disease is increased in patients with human leukocyte antigen (HLA) DR15 and HLA DR4. One study reported that approximately one-third of patients with anti-GBM antibody disease also had detectable levels of circulating ANCA antibodies, typically perinuclear antineutrophil cytoplasmic antibody (p-ANCA).

Patients typically present with fever, weight loss, malaise, cough, and dyspnea. They have pulmonary infiltrates on chest radiograph and nephritic urinary sediment on urinalysis with red blood cell, white blood cell, or granular casts. Patients may present with hemoptysis, anemia, and pulmonary infiltrates as seen in DAH (discussed subsequently). The circulating anti-GBM antibody can be detected in the blood by enzyme-linked immunosorbent assay. Without treatment, anti-GBM antibody disease has a very poor prognosis, but the prognosis is markedly improved with effective treatment with corticosteroids and cyclophosphamide. Severe cases are also treated with plasmapheresis-plasma exchange. An observational study of patients with combined ANCA and anti-GBM antibody disease found that patients who required renal replacement therapy did not return to adequate renal function despite aggressive treatment with steroids, immunosuppression, and plasma exchange.

Microscopic Polyangiitis

Microscopic polyangiitis is another ANCA-associated vasculitis that can result in pulmonary hemorrhage, hemoptysis, and respiratory failure. The vasculitis affects small-caliber arterioles, venules, and capillaries. The p-ANCA is associated with antibodies directed against myeloperoxidase, but the titer does not appear to have any prognostic implication. Common clinical manifestations of p-ANCA-related pulmonary disease include dyspnea, sinusitis, cough, fever, skin lesions, hypertension, arthralgias, hemoptysis, acute renal failure, and anemia. DAH (discussed subsequently) may also be present. Radiographic findings include nodules (which may be cavitary), ground glass opacities, fibrotic changes, and possible honeycombing. A retrospective evaluation of 65

patients with ANCA-related pulmonary vasculitis reported that acute respiratory failure requiring mechanical ventilator support, ICU admission, and administration of blood transfusions predicted increased 28-day mortality. Treatment consists primarily of corticosteroids and immunosuppressive medications, such as cyclophosphamide or methotrexate. High-dose corticosteroids with or without plasmapheresis or plasma exchange are often used in severe cases with significant organ failure. The most common side effects associated with immunosuppressive regimens were infections and myelosuppression, which occurred in approximately 45% of the patients and were associated with an increased 28-day mortality.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a granulomatous inflammatory response seen in patients with asthma who have eosinophilia and manifest immune complex deposition in the walls of small and medium-sized arteries and veins; this syndrome results in vascular necrosis. The diagnosis of Churg-Strauss syndrome is made by the presence of 4 or more of the following criteria: asthma, peripheral eosinophilia (>10%), mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. The lung is the primary site of involvement and the skin is the secondary site. Clinical manifestations include asthma, atopic disease, fever, malaise, weight loss, upper airways disease (rhinosinusitis, rhinitis, nasal polyps), skin involvement (subcutaneous nodules, purpura, urticaria), arthralgia, myalgia, mononeuritis multiplex, abdominal complaints (pain, diarrhea, colitis, gastrointestinal bleeding), cardiac abnormalities (congestive heart failure, pericarditis, hypertension), and microscopic hematuria. Chest radiograph typically reveals patchy and transient infiltrates, but variable-sized nodules may be present. Up to one-third of affected patients may have a pleural effusion, which is typically exudative and may contain eosinophils. Chest CT findings include bilateral subpleural consolidation with lobular distribution, centrilobular nodules within ground glass opacity, or variable-sized nodules often in association with bronchial wall thickening. Patients with Churg-Strauss syndrome typically have leukocytosis with eosinophilia, an elevated erythrocyte sedimentation rate, and anemia. Approximately 50% have a positive p-ANCA level.

Treatment of Churg-Strauss includes steroids, often in combination with other immune suppressants, such as cyclophosphamide or methotrexate. The therapeutic regimen is intensified with cyclophosphamide, azathioprine, or

methotrexate when evidence indicates organ-threatening disease. Other treatments that have been used in the setting of significant organ involvement include mycophenolate mofetil, intravenous immunoglobulin, hydroxyurea, rituximab, anti-IgE therapy (omalizumab), and anti–interleukin 5 therapy.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by autoantibodies directed against phospholipid-binding plasma proteins and producing venous and arterial thromboses, loss of pregnancy, and significant morbidity and mortality. The most common antiphospholipid antibodies are the lupus anticoagulant and anticardiolipin antibodies. Antiphospholipid antibodies bind serum proteins (ie, prothrombin, various protein and phospholipid complexes, and β_2 glycoprotein I). Common clinical manifestations include livedo reticularis, valvular heart disease, thrombocytopenia, nephropathy, and Coombs-positive hemolytic anemia. Primary APS occurs in the absence of other autoimmune disease, and secondary APS is seen in the setting of autoimmune diseases such as SLE. The diagnosis of APS is made by a clinical criterion such as a pregnancy morbidity or at least one arterial, venous, or small vessel thrombosis confirmed by angiographic imaging, Doppler ultrasound, or histopathological testing. Pregnancy morbidities include an unexplained fetal death at or beyond 10 weeks; premature birth beyond 34 weeks' gestation related to preeclampsia, eclampsia, or severe placental insufficiency; or 3 or more spontaneous abortions before 10 weeks of gestation. In addition to requiring a clinical criterion, the diagnosis requires demonstration of an anticardiolipin antibody, lupus anticoagulant, or anti-β_2 glycoprotein I antibody on at least 2 occasions.

A severe form of APS with widespread thromboses involving small and medium-sized blood vessels resulting in multiple organ dysfunction or failure is termed *catastrophic APS*. This disorder is typically associated with infection, malignancy, and surgical procedures. The strategy for anticoagulation in the management of APS is controversial; some authors suggest the need for high-intensity anticoagulation with an international normalized ratio (INR) greater than 3.0, whereas others recommend a lower intensity of anticoagulation with an INR goal of 2 to 3.5 Some advocate a higher INR for those patients who demonstrate arterial thromboses compared with venous thromboses. Catastrophic APS is associated with a mortality rate approaching 50% and is often treated with anticoagulation along with corticosteroids, plasmapheresis,

and intravenous immunoglobulin.

Pulmonary involvement in APS typically is manifest as pulmonary embolism but may also include ARDS, pulmonary fibrosis, pulmonary capillaritis, and alveolar hemorrhage syndromes, including DAH (discussed subsequently). A small percentage of patients who have venous thromboembolic disease will develop more permanent pulmonary vascular changes. Patients with chronic thromboembolic pulmonary hypertension typically manifest dyspnea (either at rest or with exertion), lower extremity edema, ascites, chest pain, palpitations, and occasionally syncope. Ventilation-perfusion lung scanning is a good way to screen for the disorder, but pulmonary angiography will make the diagnosis, will reveal whether the process is amenable to surgical treatment, and will demonstrate the extent of the involvement. The definitive treatment of chronic thromboembolic pulmonary hypertension is pulmonary thromboendarterectomy. The development of ARDS is typically associated with catastrophic APS. The association of APS and pulmonary fibrosis is rare, with only a handful of patients reported in the literature.

SYSTEMIC CAPILLARY LEAK SYNDROME

The systemic capillary leak syndrome (SCLS) is a rare episodic disorder causing hyperpermeability of capillaries and resulting in leakage of fluid and proteins from the intravascular space into the interstitial space. The condition was first described in 1960. Recently, a European registry was established to help determine the causes and define treatment. SCLS is more common in the Caucasian population and typically develops in patients who are in their 50s. Although no gender predominance has been found, females manifest SCLS almost a decade earlier than do males. SCLS can result in hemodynamic derangements, edema, hemoconcentration, and hypoalbuminemia. The finding of hypoalbuminemia in the absence of albuminuria is believed to be pathognomonic for the disorder. More than 90% of patients have evidence of a monoclonal gammopathy. The registry noted that upper respiratory tract infections and menstruation appear to be triggers of SCLS in the registry patients. A wide variety of prophylactic and treatment strategies have been used, including corticosteroids, antihistamines, plasmapheresis, *Ginkgo biloba* extract, β_2 agonists, thalidomide, and intravenous immunoglobulin. A review of 252 SCLS episodes in 28 patients noted acute renal dysfunction, rhabdomyolysis, arrhythmias, pericardial effusions, compartment syndromes, pancreatitis, deep venous thrombosis, and myocardial edema as the most common manifestations.

The current treatment is largely supportive, including cautious fluid resuscitation and hemodynamic and oxygenation support as necessary.

POSTTRANSPLANT LUNG DISEASE

Immunosuppressive therapy is typically administered post organ transplant and can increase the risk for common and opportunistic infections. The lung is a frequent site of these infections and may respond to the inflammatory and immune response with the development of ARDS. The lung also may be a target for toxicity from the various immunosuppressant medications or may reflect graft-vs-host disease. When the lung is the transplanted organ, additional pulmonary complications must be considered as cause of respiratory dysfunction.

Pulmonary Complications of Lung Transplant

The pulmonary complications of single or double lung transplant include primary graft dysfunction, infection, acute cellular rejection, chronic allograft rejection or bronchiolitis obliterans syndrome, large airway complications, venous thromboembolic complications, pleural effusion, recurrence of the primary lung disease, and native lung complications (**Table 4**). Primary graft dysfunction occurs in 10% to 25% of lung transplant recipients and is the leading cause of early mortality. The condition is manifested by diffuse parenchymal infiltrates and hypoxemia with a Pa_{O_2}:F_{IO_2} ratio less than 300 in the absence of cardiogenic pulmonary edema (normal pulmonary artery occlusion pressure or <18 mm Hg), venous anastomotic obstruction, or infection. Primary graft dysfunction is associated with proinflammatory cytokines and upregulation of HLA-II expression, which increases donor specific alloimmunity and thus has some similarity to the more chronic allograft rejection or bronchiolitis obliterans syndrome. The management of primary graft dysfunction is primarily supportive and similar to the management of ARDS using low-tidal-volume, lung-protective ventilatory support strategies. As in ARDS management, the patient should receive adequate positive end-expiratory pressure per the ARDS Network nomogram, and the fluid status should be conservative rather than liberal. Infectious complications are frequent in patients post lung transplant and include bacterial, mycobacterial (both *Mycobacterium tuberculosis* and atypical mycobacteria), viral, and fungal infections. The balance of immune suppression versus rejection poses a challenge for the clinician and predisposes the patient to infectious complications when excess immune suppression prevails. Patients

with a history of cystic fibrosis will have a predilection to infection with *Pseudomonas* and mucoid strains of *Pseudomonas*. The common viral infections include cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, and community viruses such as rhinovirus, respiratory syncytial virus, parainfluenza, adeno-associated virus, and influenza A and B, including the novel H1N1 influenza A.

Table 4. Pulmonary Complications of Lung Transplant

Primary graft dysfunction
Infections (bacterial, mycobacterial, viral, fungal)
Acute cellular rejection
Chronic allograft rejection
Bronchiolitis obliterans syndrome
Large airway complications
Bronchial stenosis
Bronchial necrosis and dehiscence
Exophytic granulation tissue
Tracheobronchomalacia
Pulmonary thromboembolism
Pleural effusions
Recurrence of primary disease

Acute and chronic rejection can produce pulmonary complications and a clinical picture similar to acute infection. Acute cellular rejection may occur as soon as the first week after transplant. Patients typically present with fever, cough, dyspnea, hypoxemia, crackles on examination, patchy pulmonary infiltrates on chest radiograph, and a decrease in spirometric indices. Acute cellular rejection is diagnosed by characteristic findings of rejection on lung biopsy and is treated with increased immune suppression. Chronic rejection is manifested as bronchiolitis obliterans syndrome or obliterative bronchiolitis and is a leading cause of morbidity and late mortality after lung transplant. Chronic rejection with bronchiolitis obliterans syndrome or obliterative bronchiolitis is diagnosed by characteristic changes on lung biopsy or is suggested by the finding of irreversible decline in forced expiratory volume in 1 second coupled with the presence of air trapping on inspiratory-expiratory chest CT scans and lack of another cause. Respiratory infections with bacteria, fungi, or viruses may play a role in the cause or progression. Management typically involves an increase or change in immune suppression regimen. Additional immunosuppressive agents such as sirolimus, methotrexate, cyclophosphamide, inhaled steroids, inhaled cyclosporine, and macrolides are often used in an attempt to improve lung function.

Pulmonary Complications of Hematopoietic Stem Cell Transplant

Table 5 lists common pulmonary abnormalities seen in patients after human bone marrow or stem cell transplant. The lung is a prime target for infection (bacterial, viral, fungal, mycobacterial) associated with immune suppression after hematopoietic stem cell transplant (HSCT). Respiratory dysfunction can result from the transfusion of various blood products post transplant. ARDS can complicate infections acquired post transplant and result in significant pulmonary morbidity and mortality. Transfusion-related acute lung injury and transfusion-associated circulatory overload may be relatively common causes of infiltrates, hypoxemia, and respiratory distress, and both have an improved prognosis compared with the infectious causes of ARDS in the posttransplant period. Graft-vs-host disease in the patient following allogeneic transplant may give rise to pulmonary infiltrates or obstructive lung disease.

Table 5. Types of Lung Injury Post Human Bone Marrow or Stem Cell Transplant

Infectious complications (bacterial, viral, fungal, mycobacterial)
Acute lung injury or acute respiratory distress syndrome
Radiation- or drug-induced lung disease
Pulmonary alveolar proteinosis
Capillary leak syndrome
Pulmonary veno-occlusive disease
Transfusion-related circulatory overload
Cryptogenic organizing pneumonia
Idiopathic pulmonary syndrome
Peri-engraftment respiratory distress syndrome
Delayed pulmonary toxicity syndrome
Diffuse alveolar hemorrhage
Posttransplant lymphoproliferative disorder

DAH (see ahead) is a complication of bone marrow and stem cell transplant that presents with progressive dyspnea, cough, hypoxemia, and pulmonary infiltrates. Typically the hemoglobin concentration is decreased, but hemoptysis is actually an uncommon manifestation. DAH has been reported in 5% to 12% of bone marrow and HSCT patients and is diagnosed by finding progressively bloodier return on BAL. DAH can be associated with coagulopathy, severe thrombocytopenia, or infection in the posttransplant period. Unfortunately, the mortality rate associated with DAH is reported to be 60% to 100% despite treatment with high-dose (pulsed) steroids with or without plasmapheresis.

A subgroup of post-HSCT patients manifest typical signs and symptoms of lower respiratory tract infection with cough, dyspnea, tachypnea, and crackles along with multilobar infiltrates on chest radiograph, but despite all efforts no

identifiable causative organism or positive culture has been identified. This clinical condition is termed *idiopathic pulmonary syndrome* (IPS). IPS was proposed in 1993 and is clinically defined by the presence of widespread alveolar injury and the absence of infectious, cardiac, renal, or iatrogenic causes. Risk factors for IPS after allogeneic human stem cell transplant include prior total-body irradiation, older age of recipient, acute graft-vs-host disease, and a pretransplant diagnosis of acute leukemia or myelodysplastic syndrome. With autologous HSCT, risk factors for IPS include older age of patient, severe oral mucositis, total body irradiation or BCNU (carmustine or bis-chloroethylnitrosourea) conditioning regimen, female sex, and a diagnosis of underlying solid tumor. The pathogenesis of this disorder is complex and likely involves many factors, including soluble inflammatory molecules (ie, TNF, lipopolysaccharide, reactive oxygen species), lymphocytes, and myeloid cells. Current treatment of IPS involves supportive care with oxygen and treatment with antibiotics and moderate- to high-dose steroids. Unfortunately, the response to steroid treatment is quite variable, and an unacceptably high mortality rate is associated with this syndrome. The potential for antimediator treatment (ie, anti-TNF therapy) still requires prospective, controlled evaluation to support its use.

DIFFUSE ALVEOLAR HEMORRHAGE

DAH is a potentially lethal condition that arises from a diverse group of conditions and can result in acute respiratory failure. Pulmonary vasculitides with an associated vasculitis or capillaritis includes a large group of disorders that may give rise to DAH, but the condition can arise from noninflammatory disorders as well (**Table 6**). Most patients present with cough, dyspnea, fever, and chest pain. The majority of patients will have hemoptysis, but up to a third of patients will not cough up blood. Patients typically manifest anemia or a decreasing hematocrit level and have patchy, focal, or diffuse alveolar infiltrates on chest imaging. Some authors classify this condition as DAH associated with vasculitides and capillaritis, DAH without vasculitis, and DAH associated with another condition. It is important to recognize the condition as soon as possible and establish the diagnosis and cause of DAH. Flexible bronchoscopy with BAL is the mainstay for diagnosing this condition and evaluating for the presence of a pulmonary infection. Bronchoscopy can be used to evaluate for other potential causes of hemoptysis or bleeding from the airways. The characteristic finding of persistent or increasing blood on lavage coupled with the presence of hemosiderin-laden macrophages on examination should secure the diagnosis of DAH. Once the underlying cause is identified, specific treatment can be

provided. Treatment typically combines high-dose corticosteroids with immunosuppressive agents. Plasmapheresis or plasma exchange may have a role in the setting of pulmonary vasculitides and/or capillaritis. Several case studies have reported success with recombinant human activated factor VII, although this is an off-label use. Patients with severe DAH should receive supplemental oxygen, ventilator support as needed, and correction of underlying coagulopathies and the predisposing condition, if known. Recurrent episodes of DAH can result in interstitial fibrosis or an obstructive lung disease with emphysematous changes.

Table 6. Causes of Diffuse Alveolar Hemorrhage

Pulmonary vasculitides	**Bland pulmonary hemorrhage**	**Diffuse alveolar hemorrhage associated with other causes**
ANCA-associated vasculitides ANCA-associated granulomatous vasculitis Microscopic polyangiitis Isolated pulmonary capillaritis (ANCA positive and negative) Collagen vascular disease Systemic lupus erythematosus Rheumatoid arthritis Mixed connective tissue disease Systemic sclerosis Polymyositis Primary antiphospholipid antibody syndrome Henoch-Schönlein purpura Behçet syndrome Goodpasture syndrome (antiglomerular basement membrane disease) Idiopathic glomerulonephritis (pauci-immune or immune complex related) Microscopic polyangiitis Acute lung graft rejection Idiopathic pulmonary fibrosis Post bone marrow transplantation Myasthenia gravis Cryoglobulinemia Ulcerative colitis Thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura Drugs Diphenylhydantoin	Idiopathic pulmonary hemosiderosis Goodpasture syndrome Systemic lupus erythematosus Coagulopathies Pulmonary veno-occlusive disease Mitral stenosis and mitral regurgitation Multiple myeloma Polyglandular autoimmune syndrome Subacute bacterial endocarditis Drugs Trimellitic anhydride Isocyanate Penicillamine Amiodarone Nitrofurantoin Mitomycin Sirolimus Methotrexate Haloperidol Gold All-trans-retinoic-acid Bleomycin Montelukast Zafirlukast Infliximab	Post bone marrow transplantation Crack cocaine inhalation Systemic lupus erythematosus Cytotoxic drug therapy Radiation therapy Acute respiratory distress syndrome Sarcoidosis Pulmonary embolism High-altitude pulmonary edema Lymphangioleiomyomatosis Tuberous sclerosis Pulmonary capillary hemangiomatosis Lymphangiography Malignancy Pulmonary angiosarcoma Kaposi's sarcoma Multiple myeloma Acute promyelocytic leukemia Infections Invasive aspergillosis Cytomegalovirus *Legionella* Herpes simplex *Mycoplasma* Hantavirus Leptospirosis

Propylthiouracil		

Abbreviation: ANCA, anti–neutrophil cytoplasmic antibody.

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CHAPTER 25

Nosocomial Infectious Diseases in the Intensive Care Unit

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Key words: hospital-acquired pneumonia, ventilator-associated pneumonia, intravascular catheter–related bloodstream infection, catheter-associated urinary tract infection, *Clostridium difficile* infection, surgical site infection, invasive candidiasis, nosocomial sinusitis

EVALUATION OF NEW FEVER IN ICU PATIENTS

Approach to the Evaluation of New Fever in ICU Patients

The development of fever in ICU patients is an exceedingly common problem in the ICU. According to the American College of Critical Care Medicine (ACCM) and Infectious Diseases Society of America (IDSA) guidelines for evaluation of new fever in critically ill adult patients, any patient with a temperature 101°F or greater (≥38.3°C) is considered to have fever and should be evaluated for infection.

The most accurate methods of measuring temperature include the pulmonary artery thermistor, urinary bladder catheter thermistor, esophageal probe, and rectal probe. Other acceptable methods include the oral probe and infrared ear thermometry. The temporal artery thermistor, axillary thermometer, and chemical dot thermometer are not recommended for measuring temperature in critically ill patients.

Evaluation of new fever in ICU patients should begin with a review of the patient's history and a physical examination, followed by focused laboratory and/or radiographic testing. Microbiological tests should be ordered based on the

differential diagnosis of suspected infections rather than ordered indiscriminately.

Infection may be present in patients who are euthermic or hypothermic, particularly patients who are elderly or immunocompromised, have end-stage liver disease, are taking anti-inflammatory or antipyretic medications, have large burns, or are being administered continuous renal replacement therapies or extracorporeal membrane oxygenation.

Causes of New Fever in ICU Patients

Although fever should not be a universal trigger for initiation of antibiotic therapy, early empirical antibiotic therapy should be given to ICU patients with signs of sepsis since delay in appropriate antibiotic therapy for sepsis is associated with increased mortality in this patient population.

The most common infectious causes of new fever in ICU patients include hospital-acquired pneumonia, ventilator-associated pneumonia, intravascular catheter–related bloodstream infection, catheter-associated urinary tract infection, and surgical site infection. Other less common infectious causes include *Clostridium difficile* infection and nosocomial sinusitis.

A number of noninfectious inflammatory states may cause new fever in ICU patients, including trauma, drug-related fever, intracranial hemorrhage, hematoma, aspiration pneumonitis without infection, blood product transfusion reaction, acalculous cholecystitis, pancreatitis, venous thrombosis, neuroleptic malignant syndrome, malignant hyperthermia, and drug or alcohol withdrawal.

HOSPITAL-ACQUIRED PNEUMONIA AND VENTILATOR-ASSOCIATED PNEUMONIA

Definitions

Hospital-acquired pneumonia (HAP), or nosocomial pneumonia, is defined as pneumonia that occurs 48 hours or more after hospital admission and did not appear to be incubating at the time of admission. Ventilator-associated pneumonia (VAP) is a subtype of HAP, defined as pneumonia that develops more than 48 hours following endotracheal intubation.

Pathogenesis of and Risk Factors for HAP and VAP

The strongest risk factor for HAP is endotracheal intubation combined with mechanical ventilation, which increases the risk of HAP or VAP by 6- to 21-fold. VAP is the second most common nosocomial infection in the ICU and the most common in mechanically ventilated patients.

The presence of an endotracheal (ET) tube is by far the most important risk factor for pneumonia. The ET tube provides a direct pathway for oropharyngeal secretions that are colonized with bacteria to enter the lower respiratory tract by (1) pooling and leaking around the ET tube cuff; (2) microaspiration, which can occur during intubation itself; (3) development of a bacteria-laden biofilm within the ET tube; and (4) impairment of the cough reflex and mucociliary clearance of secretions.

Other risk factors for HAP and VAP include reintubation, supine position (potential aspiration of gastric contents), oropharyngeal colonization with pathogens, elevated gastric pH (>5), and host factors such as the severity of underlying disease, previous surgery, and antibiotic exposure.

Diagnosis of HAP and VAP

The diagnosis of HAP and VAP can be challenging due to the lack of a gold standard diagnostic test. Several clinical methods have been recommended, but none have the universally accepted sensitivity or specificity to accurately identify HAP or VAP.

Since clinical findings of HAP and VAP such as fever, purulent tracheobronchial secretions, leukocytosis, and decreased oxygenation are nonspecific, diagnostic evaluation is required any time that HAP or VAP is suspected, typically starting with the chest radiograph. Common radiographic abnormalities include alveolar infiltrates, air bronchograms, and silhouetting of adjacent solid organs. Patients who have clinical findings of pneumonia and an abnormal chest radiograph should have their respiratory tract sampled and specimens sent for microscopic analysis and quantitative or semiquantitative culture. These steps are ideally performed prior to the initiation of antibiotic therapy since antibiotic therapy reduces the sensitivity of both the microscopic analysis and culture. Respiratory tract specimens should not be submitted for culture in patients who do not have any clinical findings that suggest HAP or VAP, since tracheal colonization is common in intubated patients and does not require antibiotic treatment in the absence of clinical findings of infection. In the setting of possible infection, American Thoracic Society (ATS) and IDSA guidelines recommend obtaining

lower respiratory tract samples and also allow use of tracheal aspirates for their negative predictive value (94% for VAP).

A variety of methods are available to sample material from the lower respiratory tract, including endotracheal aspiration, bronchoalveolar lavage (BAL), nonbronchoscopic (ie, blind) BAL (also known as mini-BAL), and protected specimen brush (PSB). Endotracheal aspiration and mini-BAL are performed by advancing a catheter through the endotracheal tube until resistance is met, and a clinician is not necessary to perform or supervise this nonbronchoscopic sampling. This reduces the cost, allows specimens to be obtained quickly, and facilitates serial sampling when necessary. BAL involves the infusion and aspiration of sterile saline through a flexible bronchoscope that is wedged in a bronchial segmental orifice. A PSB is a brush that is contained within a protective sheath and designed to minimize the likelihood that the brush will be contaminated during bronchoscopy.

Bronchoscopic and nonbronchoscopic sampling have been compared in suspected VAP patients. Although BAL- and PSB-based diagnoses were associated with significantly more antibiotic-free days in one multicenter study and may lead to a narrower antimicrobial regimen and more rapid de-escalation of antimicrobial therapy, more recent evidence indicates that bronchoscopic sampling does not improve mortality, length of hospital stay, duration of mechanical ventilation, or length of ICU stay.

When samples are submitted for quantitative cultures, the currently accepted diagnostic threshold is 10^3 colony-forming units (CFU)/mL for PSB, 10^4 CFU/mL for BAL and mini-BAL, and 10^6 CFU/mL for endotracheal aspirate. Semiquantitative cultures are typically reported as pathogens isolated showing light, moderate, or heavy growth. The amount of growth that indicates VAP has not been firmly established, but semiquantitative values are reasonably considered positive when the agar growth is moderate or heavy.

The use of quantitative cultures increases the specificity of the diagnosis of HAP or VAP by distinguishing patients whose airways are colonized from those who have HAP or VAP, and fewer patients are treated with antibiotics when decisions are made based on the quantitative culture data. However, recent evidence suggests that quantitative cultures do not improve mortality, days of mechanical ventilation, or length of ICU stay compared with semiquantitative cultures.

Microbiological Characteristics of HAP and VAP

Overall, the most common pathogens that cause HAP or VAP include aerobic gram-negative bacilli and *Staphylococcus aureus*, although the most likely infecting pathogen typically depends on the duration of the patient's hospital admission and whether the patient has risk factors for multidrug-resistant (MDR) pathogens. In general, early VAP is caused by pathogens that are sensitive to antibiotics, whereas late-onset VAP is caused by MDR and more difficult to treat bacteria.

Risk factors for MDR pathogens include any of the following: (1) hospital admission for more than 1 day in preceding 90 days or residence in a nursing home or long-term facility; (2) antimicrobial therapy in the preceding 90 days; (3) immunosuppressive disease or therapy; (4) family member with MDR pathogen; (5) dialysis, IV antibiotics, chemotherapy, or wound care in preceding 30 days.

For patients with early presentation (<5 days of hospital admission) and no risk factors for MDR pathogens, the most likely pathogens causing HAP or VAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Serratia marcescens*, *Proteus* species, and methicillin-susceptible *S aureus* (MSSA).

For patients with a late presentation (≥5 days of hospital admission) or who have any risk factors for MDR pathogens, causes of HAP and VAP include the previously mentioned HAP/VAP pathogens as well as MDR bacteria including methicillin-resistant *S aureus* (MRSA), *Acinetobacter* species, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL)–producing *E coli* and *K pneumoniae*, and carbapenemase-producing *E coli* and *K pneumoniae*.

Treatment of HAP and VAP

Empirical antibiotic therapy should be initiated for suspected HAP or VAP after a lower respiratory tract culture is obtained, since delay in appropriate antibiotic therapy for HAP and VAP is associated with increased mortality.

For patients with HAP or VAP who have been in the hospital for fewer than 5 days and who have no risk factors for MDR pathogens, any one of the following empirical antibiotics is recommended: levofloxacin, moxifloxacin, ampicillin-sulbactam, ceftriaxone, or ertapenem.

For patients who have been in the hospital for 5 or more days or who have risk factors for MDR pathogens, combination empirical antibiotic therapy is

recommended, including (1) either vancomycin or linezolid, plus (2) either cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem, doripenem, or aztreonam for patients with severe allergy to penicillin or cephalosporins, plus (3) either levofloxacin, ciprofloxacin, gentamicin, tobramycin, or amikacin.

Owing to the high rate of resistance to monotherapy observed with *P aeruginosa*, combination therapy is recommended. *Acinetobacter* species respond best to carbapenems, colistin, polymyxin B, and ampicillin-sulbactam. Carbapenems are also active against ESBL-positive Enterobacteriaceae. Although MDR organisms are usually associated with late-onset VAP, recent evidence suggests that they are increasingly associated with early onset VAP as well.

Most patients with HAP or VAP respond to antibiotic therapy within 48 to 72 hours, and respiratory culture data should be reviewed by this point and a decision made whether to continue, modify, or stop antibiotic treatment. A sterile lower respiratory tract culture from an intubated patient who has not had a change in antibiotic therapy in the preceding 72 hours has a very high negative predictive value (94%) for VAP.

The recommended duration of antimicrobial therapy for HAP or VAP is 8 days, as long as the patient has a good clinical response and the causal pathogen is not a nonfermenting gram-negative bacillus such as *P aeruginosa* or *Acinetobacter* species. For HAP or VAP caused by *P aeruginosa* or *Acinetobacter* species, 14 days of antibiotic therapy is suggested because of higher relapse rates with shorter durations of treatment.

Aerosolized antibiotics are not routinely recommended for the treatment of HAP or VAP. Adjunctive aerosolized tobramycin added to IV antibiotic therapy in one trial did not improve clinical outcome but did improve microbiological eradication of pathogens from the respiratory tract. The role of inhaled antibiotics in the patient who has failed systemic antibiotics is unclear.

Ventilator-Associated Tracheobronchitis

Ventilator-associated tracheobronchitis (VAT), also known as nosocomial tracheobronchitis, is manifested by bacterial infection of the tracheobronchial tree without evidence of pneumonia. Clinical findings of VAT are similar to those of HAP and VAP, including the presence of purulent tracheal secretions,

fever, and leukocytosis; however, a new or progressive chest radiograph infiltrate is not present in VAT.

An endotracheal aspirate should be submitted for culture any time that VAT is suspected. The diagnostic threshold of quantitative culture is 10^6 CFU/mL. Treatment of VAT has been shown to decrease ICU mortality, and the recommended treatment of VAT is similar to treatment for HAP or VAP. The duration of antibiotic therapy for VAT is not well defined; however, duration of treatment similar to that used for HAP or VAP is likely adequate.

Prevention of HAP and VAP

Strategies to prevent HAP and VAP are outlined in **Table 1**.

Table 1. Prevention of Hospital-acquired Pneumonia/Ventilator-associated Pneumonia

Infection prevention and control • Educate staff about hand hygiene and isolation precautions, and ensure adherence.
Endotracheal intubation and mechanical ventilation • Avoid intubation and reintubation, if possible. • Use noninvasive positive-pressure ventilation in select patients, when possible. • Use protocols for acceleration of weaning to minimize the duration of intubation and mechanical ventilation. • Maintain endotracheal tube cuff pressure at >20 cm H_2O to minimize leakage of pathogens around the cuff into the lower respiratory tract. • Use endotracheal tubes with capacity for continuous aspiration of subglottic secretions if available. • Prevent contaminated condensate from ventilator circuits from entering the endotracheal tube and inline medication nebulizers.
Modulation of oropharyngeal and gastric colonization • Implement an oral-hygiene program for mechanically ventilated patients. • Use of oral chlorhexidine rinse has prevented HAP/VAP in select patients (eg, undergoing coronary bypass grafting), but routine use in all patients is not recommended. • Selective decontamination of the digestive tract, with or without systemic antibiotics, decreases the risk of HAP/VAP; however, it is not routinely recommended because of the concern for increasing the selective pressure for antibiotic-resistant microorganisms.
Prevention of aspiration of oropharyngeal and gastric contents • Keep patients in the semirecumbent position (30°-45°) rather than supine (0°) to prevent

aspiration, especially when receiving enteral feeding.
- Use protocols for daily interruption or lightening of sedation, and avoid paralytic agents when possible, both of which depress cough and increase risk of HAP.

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

Information taken from American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388-416.

INTRAVASCULAR CATHETER-RELATED BLOODSTREAM INFECTION

Pathogenesis and Risk Factors for Catheter-Related Bloodstream Infection

The pathogenesis of catheter-related bloodstream infection (CRBSI) is typically related to one of the following mechanisms: (1) skin microorganisms can migrate from the catheter insertion site to the external surface of the catheter and reach the intravascular portion of the catheter (more commonly seen with catheters in place for a shorter duration or percutaneous nontunneled catheters); (2) microorganisms can contaminate the infusion system, such as catheter hub(s), and subsequently the catheter lumen (more commonly seen with catheters in place for a longer duration and subcutaneously tunneled catheters); or (3) microorganisms in circulating blood from another focus of infection or from contaminated infusate (eg, IV medications) can attach to the intravascular portion of the catheter, which occurs rarely.

Preventive measures that have been shown to reduce the incidence of CRBSI include the following: (1) skin preparation with chlorhexidine (not provide-iodine solution); (2) maximal barrier precautions including a cap, mask, sterile gown and gloves, and full body drape; (3) hand hygiene before and after insertion; (4) cannulation of subclavian vein rather than internal jugular vein or femoral vein, when possible; (5) prompt removal of catheters when they are no longer needed (**Table 2**).

Table 2. Prevention of Intravascular Catheter-Related Bloodstream Infection

Educate and train health care personnel who insert/maintain catheters.
Select appropriate catheter sites.

- Avoid femoral vein for CVC access. Use subclavian site, rather than jugular or femoral

site, to minimize infection risk for nontunneled CVC placement. Weigh the risks and benefits of placing CVC at a recommended site to reduce infectious complications against the risk for mechanical complications. For arterial catheters, radial, brachial, or dorsalis pedis sites are preferred over femoral or axillary sites.

Follow good hand hygiene.

- Perform hand hygiene procedures (washing hands with soap and water or alcohol-based hand rubs) before and after palpating catheter insertion sites and before and after inserting, replacing, accessing, repairing, or dressing an intravascular catheter.

Use maximal sterile barrier precautions during CVC insertion.

- Use cap, mask, sterile gown, sterile gloves, and sterile full body drape, for insertion of CVC, PICC, or guide wire exchange and during axillary or femoral artery catheter insertion. A minimum of cap, mask, sterile gloves, and small sterile fenestrated drape should be used during peripheral arterial catheter insertion.

Use >0.5% chlorhexidine skin preparation with alcohol for antisepsis.

- Prepare clean skin with >0.5% chlorhexidine preparation with alcohol before CVC and peripheral arterial catheter insertion and during dressing changes. Allow antiseptics to dry prior to placing the catheter.

Follow catheter site dressing regimens.

- Use sterile gauze (replace every 2 days) or sterile, transparent, semipermeable dressing (replace at least every 7 days) to cover the catheter site. Replace catheter site dressing if the dressing becomes damp, loosened, or visibly soiled. Do not use topical antibiotic ointment/creams on insertion sites, except for dialysis catheters.

Avoid routine replacement of CVC and arterial catheters.

Promptly remove any intravascular catheter that is no longer essential.

Use alternative strategies only if rate of CRBSI is not decreasing despite adherence to above-listed strategies.

- Consider using antiseptic/antibiotic impregnated short-term CVC (chlorhexidine/silver sulfadiazine or minocycline/rifampin) in patients whose catheter is expected to remain in place >5 days.
- Consider using chlorhexidine-impregnated sponge dressings for temporary short-term catheters.

Strive for performance improvement.

- Implement bundled strategies, and document and report rates of compliance with all components of the bundle as benchmarks for quality assurance and performance improvement.

Abbreviations: CRBSI, intravascular catheter-associated bloodstream infection; CVC, central venous catheter; PICC, peripherally inserted central catheter.

Data derived from O'Grady NP, Alexander M, Burns LA, et al. Healthcare Infection Control Practices Advisory Committee (HICPAC). Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis.* 2011;52:e162-e193.

Peripheral vein catheters, peripherally placed central catheters, and tunneled central venous catheters pose less risk of CRBSI than percutaneous nontunneled central venous catheters. Other risk factors for CRBSI include longer duration of catheterization, lower ratio of nurses to patients, and the presence of underlying disease states. It is unclear whether antibiotic- and antiseptic-coated catheters may decrease the risk of CRBSI.

Diagnosis of CRBSI

The clinical manifestations of CRBSI are typically nonspecific. Inflammation at the insertion site has no predictive value, and purulent drainage from the insertion site has poor sensitivity. CRBSI should be suspected when bloodstream infection occurs in the setting of a central venous catheter with no other apparent source. When CRBSI is suspected, culture of blood and catheters should be pursued after the decision is made to either retain or replace the suspect catheters.

Paired blood cultures should be drawn from the catheter and a peripheral vein prior to the initiation of antibiotic therapy, and each sample should be labeled to reflect the time, date, and site from which the cultures were obtained. If a blood culture cannot be drawn from a peripheral vein because of limited venous access, 2 or more blood samples can be drawn through separate intravascular catheters but should not be drawn from multiple ports of the same intravascular catheter.

Because patients with CRBSI have intravascular catheters that are colonized with microorganisms, blood obtained through the catheter typically has a higher microbial density than blood withdrawn from a peripheral vein. Two diagnostic techniques for CRBSI are based on this premise: differential time to positivity and quantitative blood culture analysis. For either of these techniques, blood cultures should be drawn simultaneously from the catheter and a peripheral vein.

For differential time to positivity, the diagnosis of CRBSI is confirmed if the same organism grows from the catheter blood and peripheral blood and the catheter blood culture becomes positive 2 hours or more prior to peripheral blood culture. For quantitative blood culture analysis, the diagnosis of CRBSI is confirmed when the same organism is isolated from the catheter blood sample and the peripheral blood sample and when the colony count in the catheter blood culture is at least 3-fold greater than the colony count in peripheral blood.

In cases of true bloodstream infections, all blood cultures, whether drawn from a peripheral vein or from an intravascular catheter, are typically positive. In instances where the catheter blood culture is positive but the peripheral blood culture is negative, clinical judgment is needed to interpret such discordant results; some clinicians favor removing or exchanging the catheter, and other clinicians may prefer to obtain additional peripheral blood cultures.

Catheter tip cultures should be performed when a catheter is removed for suspected CRBSI, whereas intravascular catheter tips should not be routinely submitted for culture for every catheter that is removed. Intravascular catheter tips can be cultured via semiquantitative (roll plate) culture or quantitative broth culture (luminal flushing or sonication methods). Semiquantitative culture is performed by rolling the distal 5-cm segment of the catheter across a blood agar plate; this is the preferred method for recently inserted catheters, because the external surface of the catheter is usually colonized in this setting. Catheters in place for a longer duration may be cultured by either method. The diagnosis of CRBSI is confirmed if the same organism is isolated from the intravascular catheter tip culture and peripheral blood cultures and there is growth of more than 15 CFU from the catheter tip by semiquantitative culture or more than 10^2 CFU from the catheter tip by quantitative broth culture.

Microbiological Characteristics of CRBSI

The most common pathogens that cause CRBSI include coagulase-negative staphylococci (*Staphylococcus epidermidis*), *S aureus*, gram-negative bacilli (*E coli*, *K pneumoniae*, and *P aeruginosa*), enterococci, and *Candida* species.

Treatment and Prevention of CRBSI

The first step for treatment of CRBSI is determining catheter management. When CRBSI is suspected, catheter removal is recommended for patients with severe sepsis, hemodynamic instability, endocarditis or evidence of metastatic

infection, neutropenia, a prosthetic valve, erythema or purulent drainage from the catheter insertion site, or persistent bacteremia after 72 hours of antimicrobial therapy to which the organism is susceptible. In these circumstances, blood cultures should be drawn and intravascular catheters should be removed immediately, rather than waiting for blood culture results, which may take 24 to 48 hours. Otherwise, catheters can be left in place until the diagnosis of CRBSI is confirmed.

All ICU patients with suspected CRBSI should begin empirical antibiotic therapy immediately after cultures are obtained. Vancomycin is the recommended antibiotic because it is the most active agent against staphylococci and enterococci. Daptomycin is an alternative agent that can be used if the risk of infection with vancomycin-resistant enterococci is present. In the setting of suspected CRBSI among patients with neutropenia, sepsis, or concern for MDR organisms, additional empirical antibiotic therapy for gram-negative bacilli is appropriate. Empirical coverage for candidemia should be administered for patients with risk factors of *Candida* species infection; *Candida* species infection is discussed later.

If the diagnosis of CRBSI is confirmed, antibiotic therapy should be tailored to culture and susceptibility results, and catheters that were left in place should be removed. Catheter salvage should be considered only in select situations of CRBSI due to coagulase-negative staphylococci or gram-negative bacilli and only if no other site for vascular access is available. If the catheter is salvaged, the patient should be given systemic antibiotic therapy in combination with antibiotic lock therapy for 10 to 14 days. Antibiotic lock therapy involves placing a high concentration of an antibiotic into the catheter lumen and leaving the antibiotic to dwell for hours or days.

The recommended duration of systemic antibiotic therapy is 5 to 7 days for coagulase-negative staphylococci if the catheter is removed, 7 to 14 days for gram-negative bacilli and enterococci regardless of whether the catheter is removed or retained, and 14 days after the first negative blood culture for *Candida* species.

For patients with CRBSI due to *S aureus*, complicated infection should be ruled out in all patients given the propensity for *S aureus* to cause disseminated infection, and infectious diseases consultation should be considered. In the setting of *S aureus*, antibiotic therapy can be limited to 14 days only if all of the following criteria are fulfilled: (1) the infected catheter is removed; (2) no

evidence of endocarditis is found on transesophageal echocardiogram performed at least 5 days after onset of bacteremia; (3) no evidence of thrombus is present on ultrasonography of the vein where the catheter was located; (4) the patient has no prosthetic intravascular device; (5) no evidence of metastatic infection is found; (6) the fever and bacteremia resolve within 72 hours after starting appropriate antibiotic therapy; and (7) the patient does not have diabetes mellitus or immunosuppression. If any of these conditions are present, 4 to 6 weeks of systemic antibiotic therapy is recommended.

CATHETER-ASSOCIATED URINARY TRACT INFECTION

Pathogenesis of Catheter-Associated Urinary Tract Infection

Urinary tract infection (UTI) is the leading nosocomial infection among all hospitalized patients, and the incidence of bacteriuria associated with urinary catheterization is approximately 5% per day. However, rates of symptomatic infection are lower; fewer than 25% of patients with catheter-associated bacteriuria develop UTI symptoms.

The pathogenesis of catheter-associated urinary tract infection (CA-UTI) is most commonly related to extraluminal colonization of the urinary catheter from bacteria in the perineal region. Additionally, intraluminal infection can occur either from urinary stasis due to drainage failure or from contamination of the urine collection bag. Bacteria also form biofilms on the inner and outer surface of the catheter, and these can serve as a source of continued colonization.

Diagnosis of CA-UTI

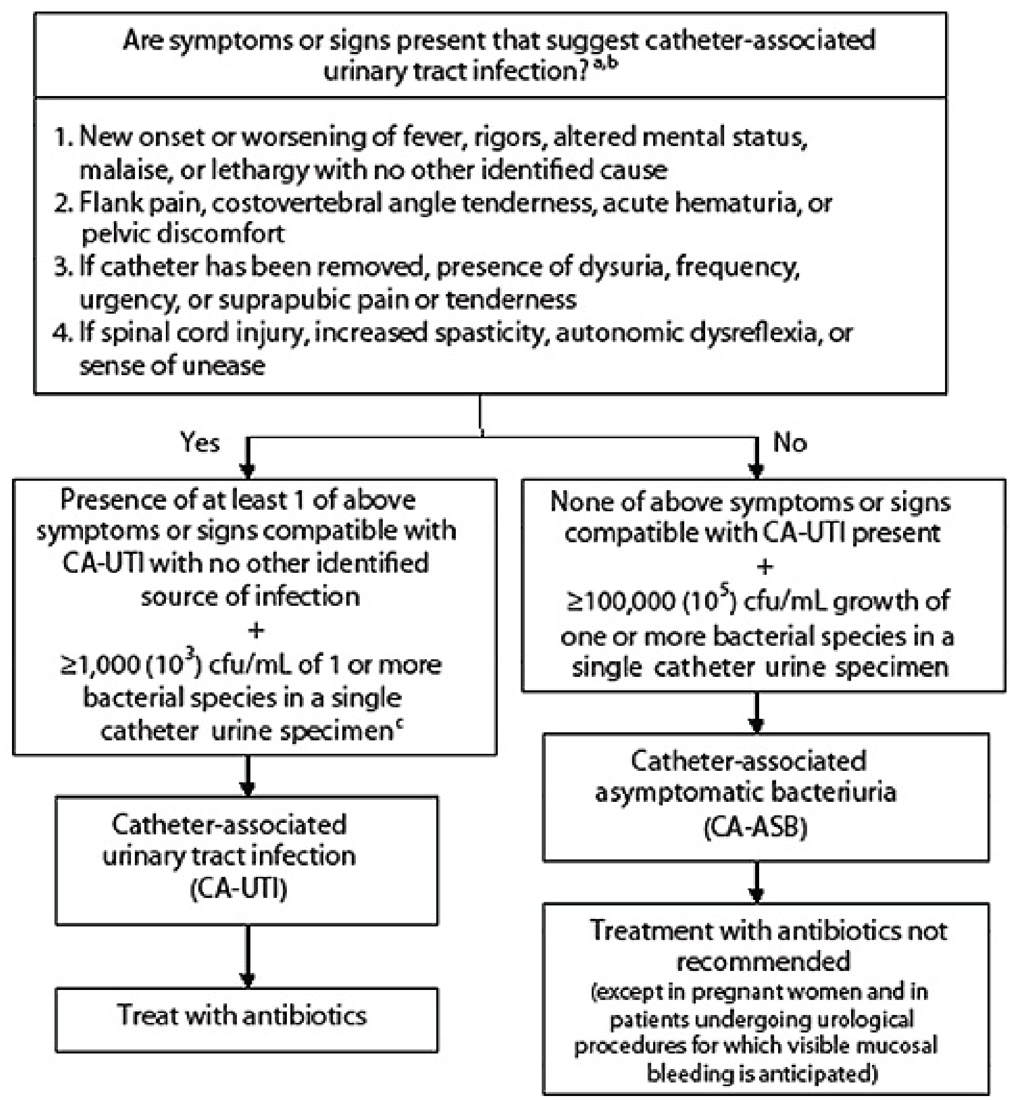
Traditional symptoms of UTI such as dysuria and urgency are rarely reported in the ICU and are not relevant in catheterized patients. Pyuria, the presence of more than 5 leukocytes per high-power field on urinalysis, is also not diagnostic of CA-UTI and cannot differentiate catheter-associated asymptomatic bacteriuria (CA-ASB) from CA-UTI; pyuria should not be interpreted as an indication for antimicrobial treatment in catheterized patients.

When clinical evaluation suggests the urinary tract as a source of infection, a urine sample should be obtained. For patients with short-term catheters (<30 days), a urine sample can be aspirated from the catheter sampling port. In patients with long-term catheters (≥30 days), the catheter should be replaced before the urine specimen is collected, so that the sample will less likely be

contaminated with organisms present on the biofilm on the surface of the catheter.

Since the presence of bacteria in a urine sample may represent contamination by bacteria colonizing the periurethral area, various thresholds for bacterial growth from a urine sample that represents true bladder bacteriuria have been suggested. According to the most recent IDSA guidelines, CA-UTI is defined as a urine culture that grows more than 10^3 CFU/mL in patients with symptoms or signs compatible with UTI, whereas CA-ASB (ie, "colonization") is defined as a urine culture that grows more than 10^5 CFU/mL in the absence of symptoms or signs compatible with UTI. Suggested symptoms and signs compatible with CA-UTI and a diagnostic approach to CA-UTI are outlined in **Figure 1**.

Figure 1. Diagnosis and treatment of catheter-associated tract infection (CA-UTI) and catheter-associated asymptomatic bacteriuria (CA-ASB)



[a]Includes patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization.

[b]Presence or absence of malodorous or cloudy urine alone should not be used to differentiate CA-ASB from CA-UTI.

[c]Or in a midstream-voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours.

Information taken from Hooton TM, Bradley SF, Cardenas DD, et al. Infectious Diseases Society of America. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:625-663.

Microbiological Characteristics of CA-UTI

E coli is the most commonly isolated pathogen in CA-UTI. Other pathogens

include enterococci, *Candida* species, *P aeruginosa*, *Klebsiella* species, and *Enterobacter* species. Patients with long-term catheters frequently have polymicrobial CA-UTI.

Treatment and Prevention of CA-UTI

Empirical antibiotics with coverage against gram-negative bacilli are recommended for ICU patients with suspected CA-UTI. If *P aeruginosa* is suspected, treatment with ciprofloxacin, ceftazidime, or cefepime may be administered. If an ESBL-producing organism is suspected based on prior cultures, antibiotic regimens are generally limited to a carbapenem.

When the diagnosis of CA-UTI is confirmed by urine culture, antibiotic therapy should be adjusted according to culture and sensitivity results. If the urinary catheter has been in place for more than 2 weeks at the time that CA-UTI is diagnosed, the catheter should be replaced, since this has been shown to hasten symptom resolution and decrease the risk of relapses.

Although the optimal duration of antibiotic treatment for CA-UTI is unknown, patients who have prompt resolution of symptoms can undergo a 7-day course of therapy, whereas 10 to 14 days of antibiotic treatment may be required for patients who respond slowly or who have concomitant bacteremia or pyelonephritis.

Treatment of CA-ASB is not recommended since antibiotic therapy in CA-ASB does not decrease complications or the incidence of subsequent CA-UTI but does promote the emergence of resistant pathogens. Exceptions include pregnant women and patients undergoing traumatic urological procedures associated with mucosal bleeding.

Strategies to prevent CA-UTI are outlined in **Table 3**.

Table 3. Prevention of Catheter-Associated Urinary Tract Infection

Appropriate urinary catheter use

- Insert catheters only for appropriate indications, and leave in place only as long as needed.
- Use alternatives to indwelling urethral catheterization in selected patients when appropriate, such as external (condom) catheters in cooperative male patients without urinary retention or bladder outlet obstruction.

Proper techniques for urinary catheter insertion

- Perform hand hygiene immediately before and after insertion or any manipulation of the catheter device or site.
- In the acute care hospital setting, insert urinary catheters using aseptic technique and sterile equipment.
- Properly secure indwelling catheters after insertion to prevent movement and urethral traction.

Proper techniques for urinary catheter maintenance

- Maintain a closed drainage system.
- Maintain unobstructed urine flow.
- Keep the collecting bag below the level of the bladder at all times.
- Use standard precautions, including the use of gloves and gown as appropriate, during any manipulation of the catheter or collecting system.
- Changing indwelling catheters or drainage bags at routine, fixed intervals is not recommended.
- Obtain urine samples aseptically.
- Routine instillation of antiseptic or antimicrobial solutions into urinary drainage bags is not recommended.
- If the CA-UTI rate is not decreasing after implementing a comprehensive strategy to reduce rates of CA-UTI, consider using antimicrobial/antiseptic-impregnated catheters.
- If obstruction occurs and it is likely that the catheter material is contributing to obstruction, change the catheter.

Quality improvement programs

- Implement quality improvement programs or strategies to ensure appropriate use of catheters, to identify and remove catheters that are no longer needed (eg, daily review of their continued need), and to ensure adherence to hand hygiene and proper care of catheters.

Abbreviation: CA-UTI, catheter-associated urinary tract infection.

Data derived Gould CV, Umscheid CA, Agarwal RK, et al. Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol.* 2010;31:319-326.

CLOSTRIDIUM DIFFICILE INFECTION

Pathogenesis of *Clostridium difficile* Infection

C difficile is an obligatory anaerobic, spore-forming, gram-positive bacillus that can produce toxin A/B. Although *C difficile* is not an invasive organism, the toxins can damage the bowel mucosa, producing symptoms ranging from diarrhea to fulminant colitis. The prevalence of severe disease has increased with the emergence of a relatively new strain of *C difficile*, NAP1/BI/027, which has a marked increase in the production of toxins.

C difficile infection (CDI) typically develops secondary to antibiotic therapy disrupting the balance of colonic flora, resulting in the overgrowth of *C difficile* bacteria. Since the spore form is resistant to alcohol and other commonly used disinfectants, pathogens can be transmitted from patient to patient by contaminated equipment or by healthcare workers with transient hand contamination.

Diagnosis of CDI

Although the principal manifestation of CDI is a watery diarrhea, clinical findings can range from asymptomatic carriage to life-threatening fulminant colitis with perforation or toxic megacolon, characterized by nonobstructive colonic dilatation associated with systemic toxicity.

The diagnosis of CDI is confirmed in the presence of symptoms, usually diarrhea, combined with (1) a stool test positive for *C difficile* toxin A/B, (2) stool culture or polymerase chain reaction (PCR) on a stool specimen positive for toxigenic *C difficile*, or (3) colonoscopic or histopathological findings revealing pseudomembranous colitis.

Testing for *C difficile* toxin A/B in stool specimens is the most commonly used method for diagnosing CDI. The enzyme immunoassay (EIA) is the most readily available test, but its sensitivity is lower than that of other diagnostic methods (60%-94%), and a negative test does not exclude CDI. The cell cytotoxicity assay, performed by assessing the cytotoxic effect of the sample stool on a mammalian tissue line, is more sensitive than EIA but has a slow turnaround and is not routinely available.

Assays that screen for the *C difficile* organism or its nucleic acid in the stool (instead of the toxin) include anaerobic stool culture, *C difficile* common antigen test, and *C difficile* PCR. Although stool culture has a high sensitivity for CDI (89%-100%), it takes 2 to 3 days and is not routinely available. With a variable

sensitivity (76%-95%), common antigen testing detects glutamate dehydrogenase, a component of *C difficile* bacteria, but requires a confirmatory test such as EIA to verify the presence of toxin A/B. *C difficile* PCR detects a gene that encodes for the *C difficile* toxin with a high sensitivity (77%-100%) and provides results within hours. PCR has become increasingly common as a diagnostic study for CDI, and some clinical guidelines suggest that PCR is superior to EIA as a standard diagnostic test for CDI.

Stool should be submitted for *C difficile* testing only if diarrhea is present, since testing stool from asymptomatic patients may yield false-positive results if asymptomatic *C difficile* stool carriage is present. In rare instances, *C difficile* testing may be performed on a nondiarrheal stool specimen if CDI is suspected and there is clinical or radiographic evidence of ileus or toxic megacolon, since these patients may not have diarrhea.

Detection of pseudomembranes on colonoscopy is highly specific for CDI, but sensitivity is low, and this test is reserved for select situations where there is a high clinical suspicion of CDI that is not confirmed by toxin assays. Computed tomography studies reveal abnormal findings in only about half of patients with CDI.

Treatment of CDI

When the diagnosis of CDI is confirmed, the inciting antibiotic agent should be stopped as soon as possible. The preferred treatment for CDI depends on disease severity, currently defined by criteria based on expert opinion. Mild to moderate disease is defined by a white blood cell count less than 15,000 cells/mm^3 and no evidence of complications, while severe disease is defined by a white blood cell count greater than 15,000 cells/mm^3 or the development of complications, including septic shock, renal failure, ileus, toxic megacolon, and bowel perforation.

For mild to moderate CDI, oral metronidazole (500 every 8 hours) for 10 to 14 days is recommended, and the preferred treatment for severe uncomplicated CDI is oral vancomycin (125 mg every 6 hours) for 10 to 14 days. These treatments are for either an initial episode or the first recurrence of CDI, because a tapered and/or pulse regimen of oral vancomycin is recommended for a second recurrence of CDI. Fidaxomicin is a recent macrocyclic antibiotic that has a narrow antimicrobial spectrum and has been shown to have similar efficacy to vancomycin for treating acute uncomplicated CDI and has been associated with

fewer relapses.

For patients who are critically ill from severe CDI, oral vancomycin is recommended at increased dosage (500 mg every 6 hours), and additional IV metronidazole is also recommended if patients have ileus or toxic megacolon since the oral antibiotics may not reliably reach the colon. Vancomycin per rectum, 500 mg every 6 hours as a retention enema, can be considered in patients with ileus. In critically ill patients with fulminant CDI, subtotal colectomy with end ileostomy should be considered, although the indication for surgery for CDI is not well defined.

Fecal microbiota transplant, a procedure in which stool is taken from a healthy individual and instilled into a patient, has shown promising results in treatment of CDI and has been suggested as therapy for a third recurrence of CDI after a pulsed vancomycin regimen.

Prevention of *C difficile* Infection

Standard precautions and contact precautions should be strictly followed by healthcare workers to minimize the transmission of *C difficile* among patients. All healthcare workers and visitors must use gloves and gowns on entry to the patient's room, and hand washing with soap and water, instead of alcohol, is preferred because the waterless antiseptic hand rubs lack sporicidal activity against *C difficile*.

SURGICAL SITE INFECTION

Definitions of Surgical Site Infection

Surgical site infection (SSI) can be classified into superficial incisional SSI, deep incisional SSI, and organ/space SSI. Superficial incisional SSI involves the skin and subcutaneous tissue, while deep incisional SSI involves the deeper soft tissues such as fascia and muscle. Organ/space SSI involves any organ or space other than incised body wall layers that was opened or manipulated during the operation (eg, intra-abdominal abscess, empyema).

Pathogenesis of and Risk Factors for SSI

Microbial contamination of the surgical site is an essential precursor of SSI. The risk of SSI is remarkably increased when the dose of contaminating

microorganisms is more than 10^5 microorganisms per gram of tissue, or if a foreign material is present at the site.

Diagnosis of SSI

The diagnosis of incisional SSI is based on physical examination findings of localized erythema, edema, tenderness, and purulent drainage at the surgical site. Superficial incisional SSIs are less likely to produce fever than deep incisional SSIs. Some patients will have erythematous changes around an incision without infection, and this may resolve with no antibiotic treatment. Although SSIs typically occur 5 to 7 days after surgery and are rarely seen within the first 48 hours, necrotizing wound infection caused by *Streptococcus pyogenes* or *Clostridium* species is evident in the first few postoperative days. Gram stain of incisional drainage should be performed in these cases to assess for infection with these pathogens.

Most organ/space SSIs are usually diagnosed by radiographic imaging such as computed tomography scan. The diagnosis of certain organ/space SSIs, such as joint space infections, requires sampling of fluid for Gram stain and culture.

Microbiological Characteristics of SSI

Although the most common pathogen involved in SSIs from clean surgical procedures is *S aureus*, the most likely infecting pathogen in a particular patient primarily depends on the patient's endogenous microbial flora, which contaminates the exposed tissues when skin, mucous membranes, and/or viscera are incised.

The common pathogens seen following most abdominal or obstetrical-gynecological operations include *S aureus*, enterococci, streptococci, coagulase-negative staphylococci, gram-negative bacilli, anaerobes, and *Candida* species. The most common pathogens seen following cardiac, thoracic, neurosurgical, orthopedic, or breast operative procedures include *S aureus* and coagulase-negative staphylococci. For patients undergoing vascular surgery procedures, the most common pathogens are *S aureus* and coagulase-negative staphylococci. For patients undergoing urological procedures, gram-negative bacilli and *S aureus* are the most common pathogens. For patients undergoing head and neck surgery, the most common pathogens include *S aureus*, streptococci, and oropharyngeal anaerobes.

Treatment of SSI

Patients with superficial incisional SSI who lack fever or tachycardia and whose erythema diameter is less than 5 cm can be managed by opening the incision site, and antibiotic therapy is not usually required. Otherwise, a short course of antibiotics, usually for a duration of 24 to 48 hours, may be indicated in addition to opening the incision site. For patients with deep incisional SSIs (including fasciitis and myositis), as well as patients with organ/space SSI, treatment includes drainage and/or debridement of infected areas in addition to antibiotics.

The choice of empirical antibiotic therapy depends on the suspected microbial flora. Empirical antibiotic therapy should be modified as indicated after results of cultures are available, usually after 48 to 72 hours. The duration of antibiotic therapy for deep incisional and organ/space SSIs is usually more prolonged than for superficial SSIs, and duration of therapy typically depends on the site of infection, adequacy of drainage, and the presence of prosthetic material which may be infected.

Prevention of SSI

Surgical antimicrobial prophylaxis (ie, “preoperative” or “perioperative” antibiotics) should be administered per the American Society of Health-System Pharmacists (ASHP) guidelines that were developed jointly by ASHP, IDSA, and other academic societies. Bactericidal levels of the antimicrobial agent should be present in serum and tissues by the time the incision is made and throughout the operation.

Antimicrobial prophylaxis should be continued for no more than 24 hours following surgery and typically can be stopped when the procedure is completed and the surgical site is closed.

INVASIVE CANDIDIASIS

Pathogenesis of and Risk Factors for Invasive Candidiasis

Candida species are the most common cause of invasive fungal infections, and candidiasis can range from mild mucocutaneous disorders to life-threatening invasive infection. The common nosocomial infections caused by *Candida* species include CRBSI, CA-UTI, SSI after abdominal procedures, and sinusitis. The risk factors for invasive candidiasis include prolonged use of broad-

spectrum antibacterial agents, presence of central venous catheters, total parenteral nutrition, renal replacement therapy in the ICU, neutropenia, previous surgery (particularly bowel surgery), gastrointestinal tract perforation or anastomotic leak, and colonization with *Candida* species.

Diagnosis of Invasive Candidiasis

The *Candida* score has been developed in critically ill patients to allow a numerical value to differentiate between *Candida* colonization and invasive candidiasis. Components of the C*andida* score are severe sepsis, total parenteral nutrition, surgery, and multifocal *Candida* colonization. Scores can range between 0 and 5, and a score of 3 or higher suggests a high risk of invasive candidiasis in the ICU.

Treatment of Invasive Candidiasis

Empirical antibiotic therapy should be initiated for patients with high risk for invasive candidiasis, and any central venous catheter should be removed. For patients with invasive candidiasis who are critically ill or who have had recent azole exposure, an echinocandin (eg, caspofungin, micafungin, or anidulafungin) is favored over fluconazole as an empirical antibiotic regimen because some *Candida* species, particularly *Candida krusei* and *Candida glabrata*, are resistant to fluconazole.

The presence of *Candida* in urine, known as *candiduria*, usually represents colonization in patients with indwelling catheters. Treatment is therefore not recommended for asymptomatic candiduria unless the patient is neutropenic. For patients with symptomatic candiduria including *Candida* cystitis and pyelonephritis, oral fluconazole is recommended. Patients who do not respond to fluconazole can be treated with oral flucytosine or amphotericin B.

The recommended duration of therapy for invasive candidiasis is for 2 weeks after clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to invasive candidiasis.

NOSOCOMIAL SINUSITIS

Pathogenesis of and Risk Factors for Nosocomial Sinusitis

Nosocomial sinusitis is defined as sinusitis that develops after hospital admission

that was not incubating at the time of admission. The incidence of nosocomial sinusitis is highest in neurosurgical patients and patients with head and facial trauma.

The development of nosocomial sinusitis is related to impaired drainage of the sinuses as a result of physical obstruction of the sinus ostia, physical irritation and local trauma to the nasal mucosa, and/or limited head mobility. This leads to sinus inflammation, edema, and fluid accumulation, which may be followed by overgrowth of bacterial flora in the sinuses.

Nasotracheal intubation and the use of a nasogastric tube have been associated with development of sinusitis. Other possible risk factors include nasal packing, high-dose corticosteroid use, facial and cranial fractures, nasal colonization with enteric gram-negative bacilli, mechanical ventilation, sedation, and unconsciousness.

Diagnosis of Nosocomial Sinusitis

Clinical findings of nosocomial sinusitis are nonspecific and difficult to assess in intubated ICU patients. When nosocomial sinusitis is suspected, radiographic imaging should be performed, and computed tomography of the paranasal sinuses is considered the imaging test of choice.

Once radiographic findings of sinusitis are noted, confirming the diagnosis of nosocomial sinusitis requires growth of 1 or more pathogens on culture of samples obtained by sinus aspiration. Given the risk of contamination of sinus aspirate specimens from nasopharyngeal or oropharyngeal flora, wide-area disinfection of the mucosa must be performed prior to sinus aspiration.

Microbiological Characteristics of Nosocomial Sinusitis

The pathogens involved in nosocomial sinusitis are typically similar to those that colonize the oropharynx in critically ill patients. The most common pathogens are gram-negative aerobic bacilli (60%), followed by *S aureus* and coagulase-negative staphylococci (30%), and *Candida* species (5%-10%).

Treatment of Nosocomial Sinusitis

Empirical antibiotic therapy for nosocomial sinusitis should provide coverage against gram-negative aerobic bacilli and staphylococci, and empirical coverage

for MRSA should be administered if MRSA has been isolated on a nasal swab. If a sinus aspirate culture was obtained, antibiotic therapy should be modified after culture results are available. The duration of antibiotic therapy for nosocomial sinusitis is not well defined; however, it is likely similar to that for HAP and VAP.

In addition to including antibiotic therapy, treatment of nosocomial sinusitis entails removal of nasogastric or nasotracheal tubes. Therapeutic sinus aspiration or drainage is recommended, if not previously done, because nosocomial sinusitis is a closed-space infection. In refractory cases where improvement is not seen with treatment, placement of an indwelling sinus catheter may be needed for continuous drainage.

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CHAPTER 26

Antibiotic, Antifungal, and Antiviral Therapies

Gourang Patel, PharmD, MSc, and Anand Kumar, MD

Key words: septic shock, infection, pharmacokinetic, pharmacodynamic

Sepsis and septic shock have been reported to be responsible for as many as 750,000 deaths annually in the United States.[1] Patient mortality related to septic shock is approximately 50% to 75% and varies in relation to immune status, presence of comorbidities, type of infecting organism, and, most important, treatment.[2] The appropriate selection of antimicrobial therapy for patients in the ICU has been revisited in recent years based on the clinical presentation. Patients with septic shock, identified by either hypotension or increased lactic acid, may require a more aggressive regimen of initial empirical therapy given recent evidence suggesting that failure to cover pathogens in a timely manner may have severe adverse consequences.

SELECTING THERAPY IN THE ICU

The selection of anti-infective therapy for patients in the ICU can be based on an initial categorization of nosocomial versus community-acquired infection. Treatment for nosocomial infection will require 1 or 2 therapies that are active against gram-negative pathogens (dependent on the hospital antibiogram), coverage for gram-positive pathogens (such as methicillin-resistant *Staphylococcus aureus* [MRSA] and/or vancomycin-resistant enterococci [VRE]), and, potentially, an antifungal therapy, based on the clinical syndrome and immune status of a patient. However, the majority of patients with critical illness due to infection have significant comorbidities (eg, diabetes, renal failure, chronic obstructive pulmonary disease) that can render the patient immunocompromised in the broader sense. Immunocompromised patients require broadened empirical therapy in much the same way as do patients with a

nosocomial source of infection or immunosuppression.

Appropriateness of empirical coverage is a critical element of antimicrobial therapy. Appropriateness includes the timeliness of drug administration based on data that are presented further in this review. In patients with septic shock, the critical time period for drug administration is as soon as shock is recognized (ideally within the first hour).[3] The following is the rationale for using the different classes of anti-infectives.

Gram-Negative Coverage

Several rationales for the use of dual gram-negative (and potentially gram-positive) coverage in the ICU are applicable when an institution demonstrates a high level of drug resistance to pathogens based on the hospital antibiogram (eg, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*).[4] The potential rationales for adding a second drug include an increased probability that one of the drugs selected will be active against the infecting organism and the possibility of clinical synergy. Although evidence indicates that some well-selected, nonantagonistic antibiotics will be active in concert with each other (eg, β-lactams and aminoglycosides) and may improve clinical outcome,[5,6] other evidence shows that certain combinations may be antagonistic and may worsen clinical outcome.[7] At a minimum, institutions that demonstrate a high level of drug resistance to monotherapy should consider adding a second gram-negative therapy for patients who have inadequate clinical response (eg, fever, hypotension). The choice of therapy is generally a β-lactam plus either an aminoglycoside or a fluoroquinolone.

Gram-Positive Coverage

The rationale for empirical gram-positive coverage in the ICU centers on the need to adequately cover MRSA and VRE infections that may be present. The selection of therapy (ie, vancomycin, linezolid, or daptomycin) is highly dependent on the local flora and the clinical site of infection (ie, lung vs bloodstream) because the properties of a drug dictate penetration and activity. For example, daptomycin becomes inactivated when in contact with pulmonary surfactant; therefore, selection of daptomycin for empirical therapy for pneumonia should be reconsidered.[8]

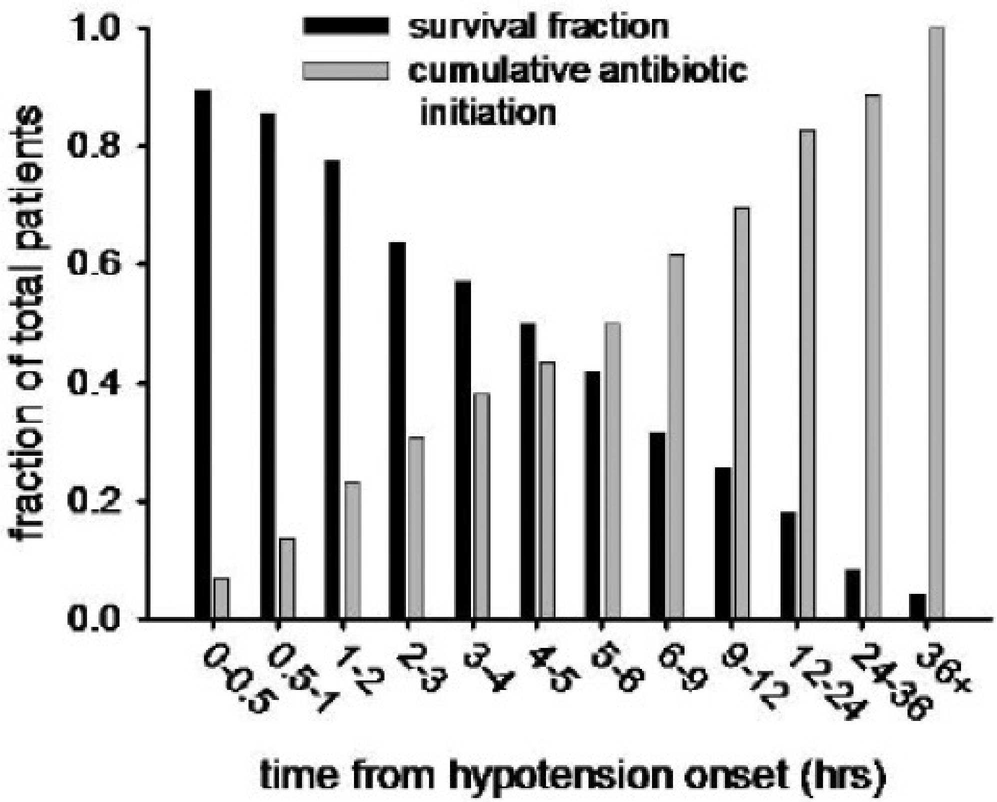
Fungal Coverage

Empirical fungal coverage for patients with septic shock in the ICU should be considered given the low toxicity of current regimens. Coverage also depends on the incidence rate of serious fungal infections at a given institution. Patients at highest risk for these types of infections generally have one or more of the following characteristics: extended ICU length of stay, renal failure, mechanical ventilation, parenteral nutrition, neutropenia, fluconazole regimen at the time of shock, recent abdominal surgery, and impaired immune function (eg, HIV, receiving steroids for systemic lupus erythematosus).[4] Once one of these risk factors has been identified in the setting of septic shock, the initiation of antifungal therapy (preferably an echinocandin) may be appropriate. Extended-spectrum azoles (eg, voriconazole) and newer formulations of polyenes (eg, liposomal amphotericin) may be reasonable alternatives given their limited toxicity.

APPROPRIATENESS AND TIME TO INITIATION OF ANTIMICROBIALS

Multiple studies have shown that initiation of empirical antimicrobial therapy with activity for subsequently isolated pathogens greatly improves the outcome of sepsis and septic shock.[9,10] However, it is clear that initiating "appropriate" microbial therapy is simply an indirect way of ensuring that excessive delays in antimicrobial therapy are avoided. Fundamentally, initiation of inappropriate antimicrobial therapy is equivalent to initiating no antimicrobial therapy at all. Several studies have supported the administration of antibiotics promptly after recognition of sepsis and septic shock.[3,11,12] Kumar and colleagues[3] demonstrated the benefits of early and appropriate antimicrobial therapy for patients in septic shock. This study, a retrospective analysis of patients presenting with septic shock, demonstrated an increase in mortality of 7.6% for every hour that antibiotic administration was delayed (**Figure 1**).

Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival



X-axis represents time (hours) following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge, and gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Reproduced with permission Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589-1596. Copyright © 2006 the Society of Critical Care Medicine and Lippincott Williams & Wilkins.

Appropriate initial empirical antimicrobial therapy in the critically ill generally includes gram-negative coverage, gram-positive coverage, and potentially, in high-risk patients, antifungal coverage. Specific clinical syndromes may also require anaerobic or antifungal therapy.

For example, patients with fungemia will require prompt administration of antifungal therapy. Patel and colleagues[13] performed a retrospective analysis of 135 candidemic patients in a tertiary medical center to determine the impact of timing of antifungals in patients with septic shock. The investigators demonstrated that the delay of antifungal therapy by 15 hours was a determinant of patient outcome. Several other authors have similarly demonstrated a substantial adverse effect of delays in initiation of appropriate antifungal therapy in such patients.[3,14] In the selection of empirical therapy for patients with septic

shock with a potential fungal pathogen, both *Candida* and non-*Candida albicans* should be targeted. Generally, historical data suggest that empirical fungal coverage for *Candida* alone was sufficient for ICU patients with suspected serious fungal infection. However, the majority of data now suggest a shift of ICU yeast isolates to non-*Candida albicans* species so that appropriate treatment requires an echinocandin, an advanced polyene, or a later-generation azole (eg, voriconazole).

In recent years, influenza has become more visible as a cause of life-threatening infection requiring ICU admission. Kumar and colleagues[15,16] reviewed recent cases of pandemic influenza A/H1N1 infection and determined that the timing of antiviral therapy affects patient outcome in this cohort. Other viral infections have similarly demonstrated evidence of therapeutic delay–dependent outcomes.

Regardless of the cause of the infection (ie, bacteria, fungus, or virus), the evidence supports early and appropriate administration of anti-infective therapy to reduce mortality, particularly for septic shock. If institutions recognize delays in appropriate and early anti-infective therapy, a process improvement team should be introduced to reduce unnecessary delays in patient care and unfavorable outcome.[11]

CLINICAL PHARMACOLOGICAL CHARACTERISTICS OF ANTIMICROBIALS

Effective treatment of an established infection requires delivery of a sufficient amount of drugs to the local site of infection for adequate time to effect a cure. Since this cannot be directly measured, in vitro parameters reflecting probability of success of antimicrobial therapy have been established (antibiotic susceptibility testing).

Susceptibility testing involves serially diluting antibiotic solutions overnight until the growth of the specific pathogen occurs. An organism is deemed susceptible to the antibiotic if the minimum inhibitory concentration (MIC) is 1/16 to 1/4 of the peak achievable serum concentration (or urine concentration if the pathogen is urinary). Despite a satisfactory MIC, antibiotic therapy can fail if the antibiotic concentrations at the target site (eg, cerebrospinal fluid, bile, prostatic tissue, pancreas, necrotic avascular tissue) are not well equilibrated with serum. Another cause of antibiotic failure is the highly protein-bound compound (eg, ceftriaxone) or failure of the drug to penetrate the bacterial cell wall (eg, β-lactam therapy in *Legionella*). An antibiotic could result in treatment

failure due to insufficient attainable concentrations in the serum (eg, drug that is not protein bound), a problem with antibiotics that are highly protein bound. Conversely, an antibiotic considered modestly effective through in vitro susceptibility testing may be highly effective clinically if well concentrated at the target site (eg, aminoglycosides for urosepsis, macrolides for intracellular *Legionella*).

Using the MIC as the sole factor in determining antibiotic therapy is problematic. With certain antibiotics (eg, aminoglycosides, fluoroquinolones), a substantial proportion of the bacteria can be inhibited or killed when the MIC is subtherapeutic (ie, postantibiotic effect). A similar effect is caused by impaired resistance to phagocytosis by the pathogens recently exposed to therapeutic antibiotic concentrations. Another reason why MIC testing has a limited association with clinical response is that the test evaluates a pathogen's response to a constant concentration of antibiotic, whereas the standard dosing is intermittent, resulting in varying concentrations at the target site. Furthermore, MIC does not distinguish between bacterial killing and inhibition of bacterial growth.

PHARMACOKINETICS AND PHARMACODYNAMICS

Clinicians must consider 2 major concepts when selecting anti-infective therapy for patients with sepsis or septic shock. One concept, termed *pharmacokinetics*, centers on how the body metabolism affects drug activity and concentration. Another concept, termed *pharmacodynamics*, concerns the concentration of the drug at the site of infection and how to best optimize this value.[17]

Pharmacokinetics encompasses the areas of absorption, distribution, metabolism, and elimination. Enteric absorption can be altered secondary to gut or bowel edema that may develop after resuscitation. Therefore, the IV route of administration is preferred in critically ill patients so there are no doubts about the amount of anti-infective therapy that reaches the circulation. Another property that can be altered in ICU patients is distribution. All anti-infective therapies have an assigned volume of distribution (V_D); V_D is simply the amount of drug administered divided by the free drug concentration in the blood (only free drug is pharmacologically active). Drugs that are restricted to the extracellular space and have low protein binding have a relatively low V_D (comparable to extracellular volume). Drugs that are intracellularly concentrated or have a high level of protein binding will have a high V_D, occasionally far in

excess of total body water. However, the apparent V_D for the patient is subject to alteration based on resuscitation efforts. The results of resuscitation efforts can dramatically alter the V_D for a given patient, often requiring an adjustment in antibiotic dosing.[18] This is particularly true for drugs with a small V_D for which the therapeutic drug concentration is only modestly higher than the MIC (eg, aminoglycosides). Another property that can be altered is the free concentration of the drug in the plasma. Medications possess variable degrees of protein binding (ie, albumin, α-acid glycoprotein) that is affected during critical illness. As the concentration of albumin decreases substantially during critical illness (ie, albumin is a negative acute phase reactant), the drug-protein binding of antibiotics is decreased, resulting in increased amounts of free drug available for activity at the site of infection. This phenomenon results in increased V_D as more drug is available to distribute to intracellular space and can result in increased elimination as well. The practice of monitoring serum levels (when possible) for therapies is therefore recommended to ensure that adequate serum levels are present throughout the dosing interval.[19,20]

Antimicrobials can be classified as having hydrophilic or lipophilic properties.[19] Hydrophilic drugs tend to not cross the cellular barrier and thus remain relatively limited to the extracellular space (aminoglycosides, β-lactams, vancomycin). Anti-infectives that demonstrate hydrophilic properties tend to have higher V_D in ICU patients, who are often volume expanded with saline and other fluids that are restricted to the extracellular space. These drugs may require increased dosing for target attainment in such patients. Lipophilic drugs are highly concentrated intracellularly and have a high degree of protein binding (macrolides, fluoroquinolones, clindamycin, rifampin, trimethoprim-sulfamethoxazole). Anti-infectives that demonstrate lipophilic properties will likely have unchanged V_D and usually do not require altered dosing in the critically ill as long as metabolism and elimination are substantially unaffected.[21]

Metabolism (ie, hepatic or renal clearance) is readily affected by sepsis or septic shock and associated organ dysfunction. Dosing adjustments need to be considered based on reports of altered hepatic and renal function of ICU patients. For example, decreased renal clearance in patients with septic shock combined with increased V_D secondary to resuscitation may require increased loading doses along with longer dosing intervals of aminoglycosides to rapidly reach microbial targets (ie, MIC) while avoiding toxicity. One strategy of ensuring that all the appropriate adjustments are made in a patient's anti-

infective therapy is anticipation of a patient's hepatic and renal function in the ICU. Serum creatinine, for example, is a trailing indicator of creatinine clearance. Acutely, urine output may be a better indicator of real-time renal clearance (assuming diuretics are not used). Most antimicrobials do not require adjustment for reduced hepatic metabolism and clearance until end-stage disease.[22]

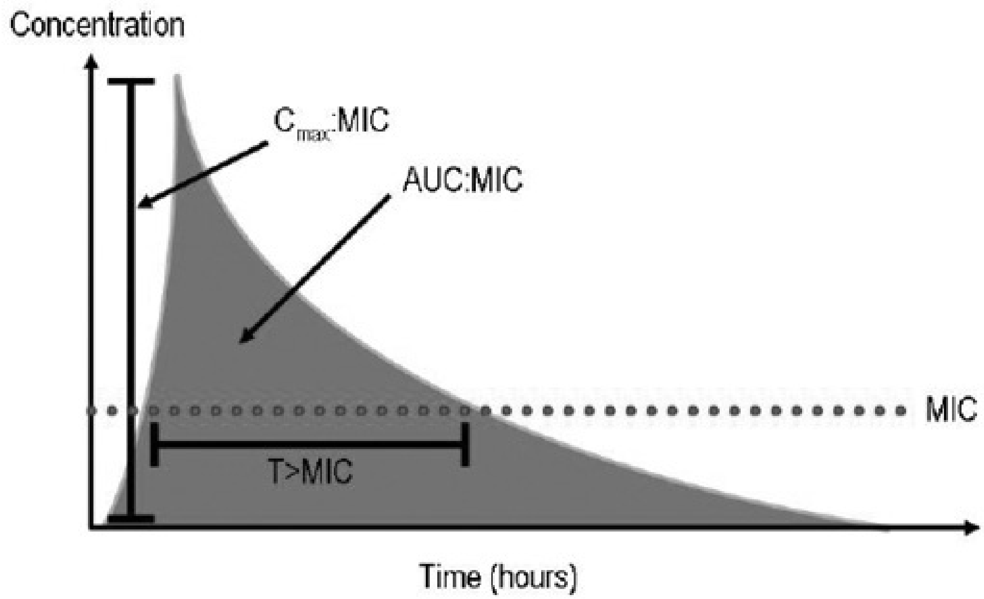
One key pharmacodynamic (PD) concept relates to the cidality of an antimicrobial. Antimicrobials can exert either cidal or static activity. These terms are assigned following in vitro examination and are correlated with clinical outcomes depending on the infecting organism. Bacteriostatic antibiotics inhibit growth of organisms, whereas bactericidal antibiotics kill the organisms. A bactericidal drug has a minimal bactericidal concentration (MBC) that is only 2 to 4 times the MIC, whereas a bacteriostatic drug has a greater than 16 times higher MBC than MIC. An alternate approach defines bactericidal drugs as having an in vitro kill rate of 99.9% within an 18- to 24-hour window, whereas bacteriostatic drugs have an in vitro kill rate of less than 99.9% within an 18- to 24-hour window.[23] Some drugs can be bacteriostatic for one group of organisms but bactericidal for another. Chloramphenicol is usually considered to be bacteriostatic. However, its well-documented utility in meningitis is attributable, in addition to its cerebrospinal fluid penetration, to the fact that chloramphenicol is bactericidal to *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, the major organisms of meningitis. Chloramphenicol is unlikely to be effective for gram-negative bacillary meningitis because it is bacteriostatic for most of those organisms. In some scenarios (eg, meningitis[7]) evidence supports the selection of a drug with one type of property versus another that can affect patient outcome.

As noted, PD relates to the concentration of drug at the site of infection. The efficacy of specific antimicrobial groups has been linked to certain PD indices. These properties of anti-infective therapy vary depending on the infecting pathogen, site of infection, drug properties, and variables affecting pharmacokinetics such as volume resuscitation and clearance. The area of focus for PD optimization depends on the class of antibiotic in question. The majority of antibiotics will be placed in 1 of the following categories: (a) time dependent, where optimal drug activity is based on the amount of time (T) spent over the MIC for the dosing interval (T>MIC), which is the case for β-lactams and carbapenems; (b) concentration dependent, where optimal drug activity is based on the maximal concentration (C_{max}) reached shortly after a drug is administered

in proportion to the MIC (C_{max}:MIC), for example, aminoglycosides; and (c) concentration and time dependent, where both the concentration and time can affect the drug activity (AUC_{0-24}:MIC, where AUC_{0-24} is the area under curve from 0 to 24 hours), for example, vancomycin.[19-21] The participation of a clinical pharmacist has been shown to improve early attainment of the antimicrobial target.[11,24]

Figure 2 demonstrates the key PD parameters of interest.

Figure 2. Pharmacodynamic parameters



Abbreviations: AUC, area under curve; C_{max}, maximum plasma concentration of antimicrobial after administration; C_{min}, minimum plasma concentration of antimicrobial before next dose; MIC, minimal inhibitory concentration of pathogen; T > MIC, duration of time that plasma drug concentration exceeds MIC of pathogen during a dosing interval.

Courtesy of Dave Nicolau.

DRUG DOSING IN SPECIAL POPULATIONS

Hypoalbuminemia

Patients admitted to the ICU with uncontrolled infection often have decreased serum albumin. Anti-infectives can have variable degrees of protein binding (albumin and α_1-acid glycoprotein are the major drug-binding proteins in the circulation) based on chemical structure and properties. This phenomenon

translates into variable drug concentrations in the serum and often results in the need to adjust dosing.[25]

Drug clearance (CL) is another property that should be appreciated by intensivists. Because clearance from the intravascular compartment is mediated by free concentration of drug, the CL is also increased with decreased protein binding, thereby leading to lower overall serum concentrations of antimicrobials over time. Anti-infectives that are more highly protein bound (>70%) and can be affected by hypoalbuminemia of critical illness include amphotericin B, echinocandins, cephalosporins (ie, cefazolin and ceftriaxone), clindamycin, daptomycin, ertapenem, rifampin, and tigecycline.[25]

Obesity

Patients who are obese (>20% of ideal body weight [IBW]) present a pharmacotherapeutic challenge in the ICU. The impact of obesity relates to metabolism and distribution parameters. The V_D is highly dependent on the lipophilic nature of a drug. Dosing based on total body weight (TBW) is generally the more accepted dosing strategy for lipophilic drugs. In contrast, for hydrophilic drugs, historical data have guided clinicians to dose based on IBW. Anti-infectives that are hydrophilic carry the potential to have a higher V_D in the obese patient, because 30% of the adipose tissue is composed of water. Therefore, anti-infectives that are hydrophilic may require an increased dose to meet target attainment in obese patients. One strategy for dosing hydrophilic antibiotics in the obese critically ill patient has been to base dosing on TBW versus IBW, which may not result in target attainment. For antibiotics that possess lipophilic properties, the dosing strategy remains unchanged in the majority of cases, and dosing based on TBW is an appropriate strategy.[26]

Continuous Renal Replacement Therapy

Renal replacement therapies (i.e. continuous veno-venous hemodialysis and filtration) introduce new challenges to medication management at the bedside. Continuous renal replacement therapy (CRRT) is very efficient at removing metabolic wastes (ie, urea, creatine) and addressing electrolyte emergencies (ie, elevated K^+). One consequence of these efficient modalities relates to the implications of antibiotic removal. Antibiotics that are hydrophilic in nature (ie, vancomycin, aminoglycoside, β-lactams) are often removed during the CRRT session, especially those that have low plasma protein binding.[27]

Loading Doses

The implementation of a loading dose (LD) can achieve the desired concentration and also takes into account the V_D ($LD = C_{desired} \times V_D$). The use of LD will help facilitate attainment of target concentration for numerous antibiotics. The maintenance dose requires adjustments to ensure an appropriate balance between efficacy and toxicity for antimicrobial therapies. As an example, the majority of hydrophilic antibiotics require increased doses and frequency intervals, whereas those that are lipophilic require minimal adjustment.[28,29] **Table 1** lists dosing strategies that can be used for dosing anti-infectives in a patient receiving CRRT.

Table 1. Antimicrobial Dosing Recommendations for Adult Patients Receiving Continuous Renal Replacement Therapies (Hemofiltration-Dialysis)

	Usual Dose	**CrCl 50-30 mL/min**	**CrCl 30-10 mL/min**	**CrCl <10 mL/min HD/PD**	**Hemofiltration (HF = see below)**
Penicillin G	2-4 MU q 4-6 h	2-4 MU q 6-8 h	2-4 MU q 8-12 h	2-4 MU q 12 h HD: 2-4 MU q 12 h PD: 2 MU q 6 h	2-3 MU q 6 h
Ampicillin	1-2 g q 4-6 h	1-2 g q 4-6 h	1-2 g q 6-8 h	1-2 g q 8-24 h HD: 1-2 g q 12-24 h PD: 250 mg q 12 h	1-2 g q 6-12 h
Ampicillin-sulbactam	1.5-3 g q 6 h	1.5-3 g q 6-8 h	1.5-3 g q 12 h	1.5-3 g q 24 h HD: 1.5-3 g q 24 h PD: 1.5-3 g q 24 h	3 g q 12 h
Piperacillin-tazobactam (extended infusion)	3.375 g q 8 h	3.375 g q 8 h	(<20 mL/min) 3.375 g q 12 h	3.375 g q 12 h	3.375 g q 8 h

				HD: 3.375 g q 12 h PD: 3.375 g q 12 h	
Cefazolin	1-2 g q 8 h	1-2 g q 8 h	1-2 g q 12 h	1 g q 24 h HD: 2 g after HD PD: 500 mg q 12 h	1-2 g q 12 h
Cefoxitin	1-2 g q 6 h	1-2 g q 8 h	1-2 g q 12 h	1-2 g q 24 h HD: 1-2 g IV q 24-48 h PD: 1 g q 24 h	1-2 g q 12 h
Cefuroxime	0.75-1.5 g q 8 h	0.75-1.5 g q 8 h	0.75-1.5 g q 12 h	0.75-1.5 g q 24 h HD: 0.75-1.5 g after HD PD: 0.75-1.5 g q 24 h	0.75-1.5 g q 12 h
Cefepime	1-2 g q 12 h, 2 g q 8 h	1-2 g q 24 h, 2 g q 12 h	0.5-1 g q 24 h, 1 g q 12 h	0.5 g q 24 h, 1 g q 24 h HD: 0.5 g q 24 h, 1 g q 24 h PD: 2 g q 48 h	1-2 g q 12 h
Aztreonam	1-2 g q 8 h	1-2 g q 8 h	1-2 g q 12 h	1-2 g q 24 h	2 g × 1, then 1-2 g q 12 h
Meropenem (extended infusion)	1 g q 8 h, 2 g q 8 h	1 g q 12 h, 2 g q 12 h	500 mg q 12 h, 1 g q 12 h	1 g q 24 h, 2 g q 24 h HD: 500 mg q 24 h, 1 g q 24 h PD: 1 g q 24 h,	1 g q 12 h, 2 g q 12 h

				2 g q 24 h	
Ertapenem	1 g q 24 h	1 g q 24 h	500 mg q 24 h	500 mg q 24 h	1 g q 24 h
				HD: 500 mg q 24 h PD: 500 mg q 24 h	
Trimethoprim-sulfamethoxazole	4-5 mg/kg per dose q 12 h (3.75 mg/kg q 6 h for PJP)	4-5 mg/kg per dose q 12 h (3.75 mg/kg q 6 h for PJP)	4-5 mg/kg per dose q 24 h (3.75 mg/kg q 12 h for PJP)	4-5 mg/kg per dose q 24 h (3.75 mg/kg q 12 h for PJP)	4-5 mg/kg per dose q 18 h (3.75 mg/kg q 8 h for PJP)
Vancomycin	15 mg/kg q 12 h	(50-20 mL/min) 15 mg/kg q 24 h	(<20 mL/min) 15 mg/kg × 1, then dose by random levels or consult pharmacist		
Gentamicin, tobramycin	See EIAD section of dosing card	See EIAD	See EIAD	<10 mL/min HD: consult pharmacist PD: consult pharmacist	Consult pharmacist
Amikacin	See EIAD section of dosing card	See EIAD	See EIAD	HD: consult pharmacist	Consult pharmacist
				<10 mL/min or PD: consult pharmacist	
Levofloxacin	500 mg q 24 h	(50-20 mL/min) 500 mg q 48 h	(20-10 mL/min) 500 mg q 48 h	500 mg q 48 h	500 mg q 48 h
	750 mg q 24 h	(50-20 mL/min) 750 mg q 48 h	(20-10 mL/min) 750 mg × 1, then 500 mg q 48 h	750 mg × 1, then 500 mg q 48 h	750 mg × 1, then 500 mg q 48 h

Acyclovir	5 mg/kg q 8 h	5 mg/kg q 12 h	5 mg/kg q 24 h	<10 mL/min or PD: 2.5 mg/kg q 24 h HD: 2.5 mg/kg q 24 h in evening	5 mg/kg q 24 h
Acyclovir central nervous system infection	10 mg/kg q 8 h	10 mg/kg q 12 h	10 mg/kg q 24 h	<10 mL/min or PD: 5 mg/kg q 24 h HD: 5 mg/kg q 24 h in evening	10 mg/kg q 24 h
Ganciclovir (induction)	5 mg/kg q 12 h	(70-50 mL/min) 5 mg/kg × 1, then 2.5 mg/kg q 12 h (50-25 mL/min) 5 mg/kg × 1, then 2.5 mg/kg q 24 h	(25-10 mL/min) 5 mg/kg × 1, then 1.25 mg/kg q 24 h	<10 mL/min: 5 mg/kg × 1, then 1.25 mg/kg 3 times a week HD: 5 mg/kg × 1, then 1.25 mg/kg post dialysis PD: ND	5 mg/kg × 1, then 2.5 mg/kg q 24 h
Ganciclovir (maintenance)	5 mg/kg q 24 h	(70-50 mL/min) 5 mg/kg × 1, then 2.5 mg/kg q 24 h (50-25 mL/min) 5 mg/kg × 1, then 1.25 mg/kg q 24 h	(25-10 mL/min) 5 mg/kg × 1, then 0.625 mg/kg q 24 h	<10 mL/min: 5 mg/kg × 1, then 0.625 mg/kg 3 times a week HD: 5 mg/kg × 1, then 0.625 mg/kg post HD	5 mg/kg × 1, then 1.25 mg/kg q 24 h

				PD: ND	
Fluconazole	200-800 mg load, then 100-400 mg q 24 h	200-800 mg load, then 50-200 mg q 24 h	200-800 mg load, then 50-200 mg q 24 h	<10 mL/min: 200-800 mg load, then 50-200 mg q 24 h	200-800 mg load, then 200-400 mg q 24 h
				HD/PD: 200-800 mg load, then 100-400 mg after each HD	
Metronidazole	500 mg q 8 h	500 mg q 8 h	500 mg q 8 h	500 mg q 8 h	500 mg q 8 h

Abbreviations: CrCl, creatine clearance; EIAD, extended interval aminoglycoside dosing; HD, hemodialysis; PCP, pneumocystis jivorceii pneumonia; PD, perioneal dialysis.

ANTIMICROBIAL THERAPIES

Anti-infectives possess various physiochemical properties and spectrums of activity that need to be taken into consideration when selecting therapy. Several classes of anti-infective therapy are reviewed next.

Antibiotics

β-Lactams

The β-lactam antibiotics include penicillins, cephalosporins, and carbapenems. The β-lactams possess hydrophilic properties, which means these agents distribute into the extracellular water. The extended-spectrum β-lactams are generally used to cover for gram-positive (eg, MRSA), gram-negative (eg, *Pseudomonas* species), and anaerobe (eg, *Clostridium perfringens*) species. The β-lactams are optimized by increasing the duration of time that the plasma concentration of the drug is above the MIC relative to the dosing interval of the drug (ie, T>MIC). The following are the thresholds for optimal results in non–critically ill patients: penicillins, 50% of the dosing interval; cephalosporins, 60% to 70% of the dosing interval; and carbapenems, 40% of the dosing interval. However, recent data suggest that 100% T>MIC may be required for optimal results in critically ill patients, particularly for patients infected with *Pseudomonas* or those with septic shock. One strategy to achieve the targets for

these 3 drug subclasses is the use of a continuous or extended infusion. Since continuous infusion would occupy a dedicated line in some instances, the general approach to drug administration is to use an extended infusion.

The majority of the agents in this drug class require dose reductions in renal failure (an exception would be ceftriaxone), as these agents are generally not protein bound. This antibiotic class does not require a loading dose; however, the clinician should consider organ dysfunction when selecting an optimal dose and frequency of therapy because accumulation of these agents in patients with renal failure can present as mental status changes and, in some instances, seizures. In addition, optimization of the dosing for β-lactams decreases the chance for development of bacterial resistance.[30,31]

Glycopeptides

The main agent in this drug class is vancomycin; agents that have been added to this class in recent years include telavancin and dalbavancin. Vancomycin has a spectrum of activity covering both methicillin-sensitive *S aureus* (MSSA) and MRSA as well as sensitive enterococci. Inferior patient outcomes for MSSA isolates relative to active β-lactams have limited their use to infections with MRSA and sensitive *Enterococcus* species. Vancomycin has hydrophilic properties and is listed as a bactericidal agent; however, in vitro and in vivo data support more of a bacteriostatic property in time-kill curves. Vancomycin exerts its activity by cell wall inhibition. The target for optimal drug activity is an AUC:MIC ratio of 400 or higher. To achieve this target, some recommend a trough of 15 to 20 μg/mL. This may require a loading dose of 25 to 30 mg/kg followed by 20 mg/kg (approximately 1.5 g in a 75-kg person) every 12 hours assuming normal renal function. Toxicities associated with drug administration are infusion-related toxicity, ototoxicity, and nephrotoxicity. The infusion-related reactions (eg, red man syndrome) are mainly secondary to histamine release and can be addressed by decreasing the administration infusion rate or by administering diphenhydramine. Ototoxicity and nephrotoxicity have been thought to be related to impurities in the drug formulation; however, recent literature suggests increased nephrotoxicity in patients requiring higher dosing of vancomycin in order to achieve the desired therapeutic targets.[19,32]

Fluoroquinolones

Fluoroquinolones are bactericidal agents with lipophilic chemical properties. Optimal dosing for fluoroquinolones can be achieved by strategies that result in

a C_{max}:MIC ratio of greater than 10 or AUC:MIC greater than 125. The ideal PD targets for fluoroquinolones can be achieved with higher doses or increased frequency. Fluoroquinolones generally have minimal toxicity; however, they have concentration-dependent central nervous system side effects (eg, mental status changes, seizures). The spectrum of activity is variable depending on the agent; however, the main targets include gram-positive (eg, *Streptococcus* species), gram-negative (eg, *Pseudomonas* species), and atypical organisms. The risk for development of resistance is decreased when higher dosing is used with decreased frequency in patients with renal dysfunction.[33,34]

Aminoglycosides

Aminoglycosides exhibit both bacteriostatic (inhibition of protein synthesis) and bactericidal (cell wall disruption) activity. The aminoglycosides have optimal activity against a broad range of gram-negative organisms (eg, *Escherichia coli*, *Pseudomonas*, and *Acinetobacter* species). These agents (particularly gentamicin) can be used in synergistic doses against gram-positive bacteria including *S aureus* and streptococci. Aminoglycosides are dosed to achieve a PD target of C_{max}:MIC ratio greater than 8 to 10. Bactericidal activity for this drug class is concentration dependent; therefore, using once-daily dosing rather than traditional multiple-day dosing (ie, 2 or 3 times daily) is recommended to most effectively achieve the PD target. In addition, once-daily dosing will be beneficial with respect to side effects. Nephrotoxicity from once-daily dosing appears to be reduced relative to multiple-daily dosing strategies. Early nephrotoxicity can be detected by the loss of potassium and magnesium similar to what is observed with amphotericin. The renal failure that typically presents later is initially nonoliguric. This renal failure has been theorized to be secondary to disruption of the aquaporin 2 channels on the kidney collecting ducts. The cause of ototoxicity has been thought to be secondary to the accumulation of drug in the inner ear causing disruption of both cochlear and vestibular apparatuses. The result may be defects in hearing and balance.[19,35]

Colistin

Colistin belongs to a class of antibiotics referred to as the polymyxins. Colistin is available as colistimethate sodium (CMS). CMS is a prodrug that requires conversion to the active moiety and also has been reported to have lower incidence of toxicity. Colistin has a narrow therapeutic window, such that the effective dose and toxicity dose are within close range of each other, specifically for nephrotoxicity. The CMS moiety is a prodrug and therefore requires

conversion to active colistin for its antibacterial properties. If used, colistin should be initiated with a loading dose prior to a scheduled dosing regimen to ensure adequate concentrations during therapy. Colistin can be used in combination with other antibiotics (eg, carbapenems, tigecycline) for the treatment of resistant gram-negative organisms (eg, *Pseudomonas* and *Acinetobacter* species and *Klebsiella pneumoniae*). Monotherapy with colistin therapy is generally discouraged due to the development of bacterial resistance.[36,37]

Macrolides

Macrolide antibiotics are generally considered bacteriostatic in activity. These drugs are highly lipophilic and have a large V_D. Macrolide dosing is targeted to achieve optimal effects based on a higher AUC:MIC. Macrolide antibiotics provide coverage against gram-positive organisms (eg, *Streptococcus* species) and atypical organisms (eg, *Legionella*). In general, these antibiotics are used to treat community-acquired infections. The toxicities with macrolides are minimal; however, several macrolides have well-documented effects on electrocardiogram (eg, QT interval prolongation) based on intrinsic activity on the channels within the myocardium. This is of particular concern with erythromycin.[21]

Daptomycin

Daptomycin is a lipopeptide antibiotic that has bactericidal activity for a wide variety of gram-positive pathogens. Daptomycin is used for susceptible and resistant gram-positive organisms (eg, MRSA and VRE). Daptomycin is dosed to achieve the targets of C_{max}:MIC. The drug is dosed once daily and needs to be adjusted for renal dysfunction. The dosing is variable based on the indication and target organism as follows: empirical skin and soft tissue, 4 mg/kg; MSSA and MRSA, 6 mg/kg; and VRE, 8 mg/kg. The dosing for VRE is based on initial in vitro time-kill data. The main caution with indications for this agent is in suspected gram-positive pneumonia, because pulmonary surfactant can antagonize the activity of daptomycin. The main side effect associated with daptomycin is elevation of creatine phosphokinase. This occurs through direct muscle tissue toxicity when the drug is used in high doses and with prolonged duration of exposure.[19,21]

Tigecycline

Tigecycline is a newer-generation tetracycline anti-infective that is used for both resistant gram-positive and selected gram-negative infections. The antibiotic is bacteriostatic in nature and requires a loading dose and maintenance dose regimens. Tigecycline has coverage against resistant gram-positive infections (eg, MRSA and VRE) and selected gram-negative infections (eg, *Acinetobacter* and *Stenotrophomonas*); however, the types of infections for which the drug has been researched and approved need to be emphasized. The drug is indicated for complicated skin and soft tissue infections; however, a trial in patients with suspected or documented MRSA pneumonia was halted early secondary to increased mortality in the tigecycline group. One hypothesis of this observation is based on tigecycline pharmacokinetic properties and extensive protein binding, which limited tissue penetration. The main side effects reported with tigecycline use have been gastrointestinal (ie, diarrhea).[19]

Linezolid

Linezolid is in the class of oxazolidinones and is used for resistant gram-positive infections (eg, MRSA and VRE). Linezolid is a bacteriostatic antibiotic. The PD parameter that predicts optimal activity is AUC:MIC. The dosing of the drug is standard regardless of the type of organism. The main side effects reported are thrombocytopenia, serotonin syndrome in patients taking concomitant selective serotonin reuptake inhibitors or monoamine oxidase inhibitors, and peripheral neuropathies associated with prolonged duration of drug exposure. Thrombocytopenia is hypothesized to be secondary to direct suppressive effects on the bone marrow and is generally observed after at least 10 days of therapy.[18]

Table 2 lists the major antimicrobial groups with key PD characteristics and antimicrobial activity.

Table 2. Optimization of Antibiotic Therapy

Antibiotic Class	Mechanism of Action	Chemical Property	Pharmacodynamic Parameter	Antimicrobial Coverage	Toxicity
β-lactams	Inhibition of cell wall synthesis via binding PCN-binding protein	Hydrophilic	T > MIC for dosing interval and target attainment with extended infusion PCN 50% Cephalosporins 60%-70%	Extended-spectrum β-lactam and later-generation cephalosporins *Pseudomonas aeruginosa*	Renal ad needed Accumula leading to seizure th Thrombo
Carbapenems			T > MIC for dosing	ESBL producing	

			interval for 40% of time attained with extended infusion	*Escherichia coli* or *Klebsiella* species	
Aminoglycosides	Inhibition of ribosomal protein synthesis 30s unit and cell wall synthesis	Hydrophilic	C_{max}/MIC ratio of 8-10 for maximal target attainment with once-daily dosing	*P aeruginosa* *Acinetobacter baumannii* *Klebsiella* producing carbapenemase	Ototoxicit Nephroto Smaller s profile wi daily dos monitorin
Quinolone	Inhibition of DNA gyrase and topoisomerase	Lipophilic	AUC/MIC and Cmax/MIC, both concentration and time dependent	*P aeruginosa* Atypical coverage	Lowering threshold (selected
Glycopeptide	Inhibition of cell wall synthesis via dAla, dAla	Hydrophilic	AUC/MIC ratio of ≥400 Target attainment with trough concentration of 15-20 µg/mL	MRSA	Minimal, increasin used for t attainmer nephroto reported
Lincosamides	Inhibition of ribosomal protein synthesis	Lipophilic	T > MIC	Gram-positive–induced toxic shock	None
Linezolid	Inhibition of ribosomal protein synthesis at 23s	Hydrophilic	T > MIC for 30%-80% of dosing interval	MRSA and VRE	Thrombo (>10 d of Lactic ac Drug-inte with SSR
Tigecycline	Inhibition of ribosomal protein synthesis at 30s	Lipophilic	AUC/MIC	MRSA, VRE, *A baumannii*, and *Proteus* species	GI: N/V/D
Daptomycin	Binding to cell wall resulting in depolarization via release of potassium, which arrests	Hydrophilic	C_{max} > MIC Targets differ for MRSA and VRE	MRSA and VRE	Elevation

	DNA/RNA synthesis				

Abbreviations: AUC, area under curve, C_{max}, maximum plasma concentration of antimicrobial administration, CPK, creatine phosphokinase; dAla-d, alanine cell wall component; ESBL, extended spectrum beta-lactamase producing organism; GI:N/V/D, gastrointestinal nausea/vomiting/diarrhea; MIC, minimal inhibitory concentration of pathogen; MRSA, methicillin-resistant *Staphylococcus* aureus; PCN, penicillin; SSRI, selective serotonin reuptake inhibitor; T > MIC, duration of time that plasma drug concentration exceeds MIC of pathogen during a dosing interval.

Antifungals

Polyenes

The antifungals are divided into 3 main classes: polyenes, azoles, and echinocandins. The prototypical polyene antifungal is amphotericin deoxycholate, which is rapidly fungicidal for most pathogenic fungi. Later formulations of this were combined with different delivery systems to limit toxicities. The additional formulations of this are amphotericin colloidal dispersion (ABCD), amphotericin lipid complex (ABLC), and liposomal amphotericin (LAMB). All dosage preparations of amphotericin are active via disruption of the fungal cell wall membrane via ergosterol membrane synthesis. The disruption of this cell membrane results in loss of potassium and magnesium and death of the pathogenic organism. The spectrum of activity of polyenes is very broad (eg, yeast and mold species). These drugs can be used for empirical treatment of almost all fungal infections. The toxicities of the polyenes are generally infusion-related reactions, hepatotoxicity, and nephrotoxicity. The infusion-related reactions are thought to be secondary to histamine release; ABLC and LAMB tend to have less association with this phenomenon. The occurrence of nephrotoxicity is highest to lowest in the following order: amphotericin deoxycholate > ABCD > ABLC > LAMB. This toxicity appears to affect the kidney collecting tubule and results in wasting of the electrolytes potassium and magnesium. The hepatotoxicity is secondary to an interaction between the lipid formulations (ABLC and LAMB) with metabolism requiring hepatic transformation so that active amphotericin can be released into the bloodstream.[38,39]

Azoles

The newer-generation azole antifungals (eg, voriconazole and posaconazole) can be used for empirical coverage against yeast and mold fungal species. The

mechanism by which the drugs exert their activity is via inhibition of the fungal cytochrome P450 14-methyl lanosterol demethylation. The main caution in selection of therapy is to ensure there are no contraindications related to drug-drug interactions, which occur not infrequently with this class of antifungals. Most of these agents are metabolized via the CYP 450 system and involve reactions mediated via the 3A4 system.[38,39] These agents are fungistatic with respect to yeast and for this reason are not the preferred agents for critically ill patients and those with septic shock.

Echinocandins

The echinocandins are an excellent alternative for fungal coverage in the ICU given their broad cidality and low toxicity. The echinocandins exert their activity via inhibition of the fungal cell wall β(1,3)-D-glucan component. The spectrum of activity of echinocandins includes both yeast and mold species. The 3 available medications in this class are caspofungin, anidulafungin, and micafungin. All 3 preparations have variable dosing schemes, but each requires a loading dose and maintenance dosing. This drug class has a minimal side effect profile; however, a screening of drug-drug interactions should be performed.[38,39]

Antivirals

Antiviral therapies should be used for empirical therapy when viral meningitis or influenza is suspected. The drug classes can be subdivided for use in the ICU into 2 major categories: antiherpes and anti-influenza drugs.

Antiherpes Drugs

The antiherpes drugs that can be used in the ICU are acyclovir, foscarnet, and ganciclovir. The drugs exert their mechanism of action by targeting viral DNA replication. The dosing of medication and duration of therapy depend on the viral infection and agent. All of the agents possess inherent side effect profiles: acyclovir (especially in renal dysfunction) can result in mental status changes, foscarnet can lead to infusion-related reactions and nephrotoxicity, and ganciclovir therapy can result in thrombocytopenia.[40]

Anti-Influenza Drugs

The anti-influenza drugs include the older M2 ion channel inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). The former are not active against 2009 pandemic influenza A/H1N1

or influenza B. The latter are active for both of these but lack consistent activity for seasonal influenza H1N1. The neuraminidase inhibitors that are used the most inhibit viral neuraminidase, the enzyme responsible for cleaving sialic acid from the viral cell membrane leading to release of the virus. The agents all have variable dosing strategies and use based on availability. The overall side effect profile for these agents is favorable based on current literature reports.[40]

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CHAPTER 27

Infections in the Immunosuppressed and Immunocompromised Patient

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Key words: immunosuppression, immunocompromise, antimicrobial therapy, neutropenia, organ transplant, bone marrow transplant, asplenia, complement deficiency

Over the last decades, the number of immunocompromised patients has continued to increase in parallel with improvements in transplantation science and alongside the development of numerous new classes of immunosuppressive agents that offer novel therapy for a wide range of diseases. This growing population, however, also represents an increasing number of at-risk hosts. Of great concern, the incidence of serious infections and severe sepsis has clearly increased over time.[1] Intensivists require a succinct clinical approach to assess a patient's immunological function and subsequent risk for infection in order to prescribe timely and appropriate therapy.

Several medical advances have contributed to the increase in infections: Advances in chemotherapeutic regimens and stem cell transplantation have improved outcomes among patients with solid organ and hematological malignancies.[2] Along with such advances, however, rates of serious infections have increased.[3-5] The volume of organ transplants (which entail concomitant long-term immunosuppressive drug therapy) and survival rates have dramatically increased since the 1960s. For example, the Global Observatory on Donation and Transplantation estimates that in 2014, approximately 119,873 solid organ transplants were performed worldwide.[6] As a result, the frequency of post transplant infections and malignancies has risen, becoming the main impediment to survival after transplant.[7,8] Supportive therapies such as total parenteral nutrition, dialysis, blood transfusions, and advanced ICU support, which allow patients with chronic diseases and/or immune dysfunction to

survive for extended periods, also contribute their share to the increase in infections.

For clinicians and their patients, recognition of the immunocompromised state is imperative. Infections in such patients can involve unusual organisms that require atypical pharmacological therapy. In addition to having increased susceptibility to common community-acquired and nosocomial pathogens, immunocompromised patients are vulnerable to opportunistic pathogens (eg, *Cryptococcus*, *Candida*, and *Aspergillus* species) and to reactivation of endogenous but latent organisms (eg, herpes viruses, *Toxoplasma gondii*, and *Pneumocystis jirovecii*) (**Table 1**).

Table 1. Common Causes of Immunosuppression and Major Infections in Immunocompromised Patients

Immunosuppression		**Major Infections and Their Cause**			
Defect	**Cause**	**Pneumonia**	**Central Nervous System Infection**	**Mucocutaneous Infection**	**Disse Infect**
Neutropenia	Leukemia Chemotherapy (cyclophosphamide, cytosine arabinoside, doxorubicin) Total-body radiation Idiopathic drug effect Aplastic anemia	Enteric gram-negative bacilli *Pseudomonas aeruginosa* *Staphylococcus aureus* *Aspergillus* species	Enteric gram-negative bacilli *Aspergillus* species *Mucormycosis* species	HSV VZV	*Asper* specie Other
Cell-mediated	Hodgkin lymphoma Corticosteroid use Chemotherapy (azathioprine, vincristine, bleomycin) HIV, CMV, or Epstein-Barr virus infection Protein-calorie malnutrition	*Pneumocystis jirovecii* *Legionella* species Herpesvirus (CMV, HSV, VZV) Adenovirus Histoplasmosis Coccidiomycosis	*C neoformans* *Toxoplasma gondii* *Listeria monocytogenes* Human herpes virus 6	HSV VZV CMV *Candida* species	CMV VZV *Mycol avium intrac*

		Cryptococcus neoformans			
Humoral	Multiple myeloma Chronic lymphocytic leukemia Chemotherapy (cyclophosphamide, methotrexate, azathioprine) Splenectomy	*Streptococcus pneumoniae* *Haemophilus influenza* Enteric gram-negative bacilli	*S pneumoniae* *H influenza* *Neisseria meningitidis*	—	—
Complement	Congenital deficiency Systemic lupus erythematosus Multiple myeloma	—	*N meningitidis*	—	*N men* *Neiss gonor*

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Furthermore, infection with these pathogens in the immunocompromised patient can present with minimal signs and symptoms or with atypical features in unusual locations. This can considerably delay the diagnosis if the presence of the immune defect is not appreciated. Although the risk of mortality is higher in this population, given the underlying immunosuppression and the unusual nature of the involved organisms, outcome can be optimized by early diagnosis and aggressive treatments with specific pharmacotherapy.

A basic understanding of immunological host defenses is required to appreciate the likely cause of infection in the immunocompromised patient. Nonspecific (nonimmune) host defenses, like intact integumentary barriers, can be breached (eg, burns, severe eczema, denudation of epitheliums due to chemotherapy, central lines), breaking the primary host defense barrier against the normal microbiome. Specific immune defects can be categorized into 4 clinically relevant groups (**Table 1**). Neutropenia, or the absence of polymorphonuclear leukocytes (PMNs), the cells responsible for phagocytosis and killing of extracellular microbes, is the most common defect of PMN function. The second immune-defect group involves cell-mediated immunity, processes by which intracellular pathogens as well as malignant and virus-infected cells are eliminated by monocytes and macrophages with help from T-lymphocytes. The

third clinically relevant category involves the humoral arm of the immune system, B-lymphocytes and clonal antibody production against foreign antigens. Finally, defects in the complement cascade, the major amplification pathway of the normal immune system, also represent an important immune defect.

To approach infections in the immunocompromised patient, the clinician should consider a few principles in order to narrow the initial diagnostic possibilities and target empirical therapy for the appropriate etiological categories (**Table 2**).

Table 2. Antimicrobial Therapy in Immunocompromised Patients

Antimicrobial Agent	Comments
Antibiotics	
Third-generation cephalosporins	Only ceftazidime and cefoperazone sodium are appropriate for coverage of *Pseudomonas aeruginosa.* Inappropriate as single agents for organisms capable of producing inducible β-lactamases.
Fourth-generation cephalosporins	Modestly enhanced gram-positive activity and increased gram-negative activity (due to improved stability to inducible β-lactamases).
Advanced cephalosporins: ceftaroline and ceftobiprole	Approved for skin and soft tissue infections and nosocomial pneumonia: have activity against gram-positive and gram-negative organisms. Have activity against MRSA and resistant pneumococcus. Although having activity against gram negatives, susceptible to amphotericin C β-lactamases.
Extended-spectrum β-lactams	Because of the potential for resistance, piperacillin, azlocillin sodium, or mezlocillin sodium should be administered with either an aminoglycoside, a fluoroquinolone, or a third-generation cephalosporin. Ureidopenicillins (piperacillin, azlocillin, and mezlocillin) have a greater pseudomonal, enterococcal, and anaerobic activity than do carboxypenicillins (carbenicillin and ticarcillin).
Penicillin β-lactamase inhibitor combinations	Piperacillin-tazobactam exhibits increased activity against *Staphylococcus aureus*, anaerobes, and gram-negative bacilli compared with piperacillin alone. The addition of clavulanate similarly broadens the activity of ticarcillin.
Carbapenems	Imipenem-cilastatin, doripenem, and meropenem are the agents with the broadest activity and can be combined with an aminoglycoside if *Pseudomonas* is present. However, data suggest that monotherapy with these agents is effective.

Aminoglycosides	Historically preferred agents, in combination with antipseudomonal β-lactams, for neutropenic fever and sepsis. Recent data suggest that toxicity is decreased and efficacy is preserved with once-daily doses.
Quinolones	Ciprofloxacin, levofloxacin, and moxifloxacin appear to be effective alternatives to aminoglycosides for the treatment of neutropenic fever or sepsis, particularly in patients with renal failure.
Glycylcyclines: tigecycline	New class of antibiotic similar to tetracyclines with bacteriostatic activity against gram-positive, gram-negative, and anaerobic organisms. Active against MRSA, VRE, *Acinetobacter baumannii*, and ESBL-producing organisms *Klebsiella* and *Escherichia coli.* No activity against *Pseudomonas* or *Proteus.* Approved for complicated intra-abdominal infections.
Vancomycin, daptomycin and telavancin	All cover gram-positive cocci, including *Enterococcus* and *Staphylococcus* species. Vancomycin should be used for treatment of neutropenic fever when a specific risk factor, including a high incidence of MRSA, exists. A major concern is nosocomial infection with ampicillin- and vancomycin-resistant *Enterococcus.* Daptomycin has a high degree of cidality for gram-positive pathogens and appears to be an effective alternative to vancomycin. However, pulmonary activity of this agent is suboptimal, and it should be avoided for pneumonia. Other novel agents such as quinupristin-dalfopristin and linezolid are generally bacteriostatic agents and are not optimal for therapy of immunosuppressed patients. Telavancin was recently approved for skin and soft tissue infections and nosocomial pneumonia and was found to be noninferior to vancomycin in clinical trials. No distinct advantage has been found for its use.
Antifungals	
Amphotericin B	Most reliably effective treatment for most fungal infections; liposomal and colloidal forms with decreased renal toxicity are available. Varying doses are used for different clinical infections and formulations.
Fluconazole	Effective for thrush and *Candida* esophagitis; some evidence supports the use for *Candida* infection of intravascular catheters; maintenance therapy for cryptococcal meningitis.
Itraconazole	Broader activity than fluconazole; possibly of particular utility in *Candida* infection of biliary system.
Voriconazole,	Highly active for *Candida* species.

posaconazole	Current literature suggests that this is the preferred therapy for *Aspergillus* infections
Echinocandins	Group includes caspofungin, micafungin, and anidulafungin; wide spectrum of activity including *Pneumocystis jirovecii* but ineffective for *Cryptococcus*.
Antivirals	
Acyclovir	Indicated for mucocutaneous herpes, disseminated herpes zoster, or primary varicella at varying doses.
Ganciclovir	Indicated for CMV retinitis and other infections in HIV-infected patients (utility of treatment of pulmonary CMV isolate from AIDS patients with other pulmonary pathogens is unclear); also indicated for CMV pneumonitis in patients receiving bone marrow transplant and other solid organ transplant. Varying doses and durations are used for different infections. May have utility for other herpes viruses (simplex or zoster).
Antiparasitics	
TMP-SMX	Optimal therapy for *P jirovecii*: 15-20 mg/kg/d in 4 divided doses for 21 days (if PaO_2 <70 mm Hg on room air, corticosteroid therapy should be instituted).
Pentamidine	Alternative treatment of *P jirovecii* pneumonia; more side effects than TMP-SMX.
Sulfadiazine + pyrimethamine + folinic acid	Optimal therapy of cerebral toxoplasmosis; chronic suppressive therapy should follow. Use corticosteroids (dexamethasone, 4 mg every 6 h) if significant brain edema or mass effect.

Abbreviations: CMV, cytomegalovirus; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

First, the likelihood of a given opportunistic infection is related to the nature of the immune defect. Deficiencies of humoral immune function (including asplenia and complement deficits) predispose patients to infections with encapsulated bacteria. Cellular immune dysfunction (HIV, lymphoma, corticosteroid therapy) predisposes patients to infection with more unusual organisms. These include atypical bacteria such as *Listeria* and *Nocardia*; mycobacteria; fungi including *Cryptococcus*, *Candida*, and *P jirovecii*; viruses, particularly herpes viruses; and parasites such as *T gondii.* Neutropenia secondary to acute leukemia, cytotoxic chemotherapy, or aplastic anemia and chronic neutrophil dysfunction such as seen in chronic granulomatous disease are associated with increased infections by pyogenic bacteria (eg,

Staphylococcus aureus, enteric gram-negative rods, *Pseudomonas aeruginosa*) and fungi (eg, *Candida*, *Aspergillus*).

Second, the probable cause of infection is linked to the severity of the immune defect. Infection due to neutrophil depletion following chemotherapy is unusual with absolute neutrophil counts (ANCs) greater than 500/µL but is almost predictable as ANC falls below 100/µL.[9] Similarly, although prednisone can broadly suppress the immune system, *P jirovecii* infections are rare, unless doses of 15 to 40 mg/d are administered for at least 3 months (without prophylaxis).[10,11] Although the risk of opportunistic infections increases as CD4 counts in HIV-infected patients fall below 800/µL, such infections are uncommon while the CD4 count exceeds 300/µL. Only 5% of HIV-associated opportunistic infections occur above 300/µL.[12] Various opportunistic infections including *Candida*, *P jirovecii*, and *Mycobacterium avium-intracellulare* become sequentially more common as the CD4 count falls to less than 100 cells/µL.

Third, the duration of the immune deficit helps define the probable infecting agents. As a classic example, bacterial infection is common early in the neutropenic period, whereas fungal infections become increasingly important after the first weeks of neutropenia. In organ transplant patients, prolonged immunosuppression leads to a predictable evolution of infection risk.[8,13] Within the first month post transplant, patients are at risk for the same early postoperative infectious complications seen in immunocompetent patients with similarly extensive surgery. Between the first and sixth months post transplant, infections with various fungi (eg, *Cryptococcus*, *Candida*, *Aspergillus*, *P jirovecii*) and viruses (eg, cytomegalovirus [CMV], Epstein-Barr virus [EBV], varicella zoster virus [VZV] dissemination, non-A non-B hepatitis) dominate. After 6 months, the risk of opportunistic infections decreases as immunosuppressive regimens are tapered. Despite decreased immunosuppression, however, there remains some chronic risk of infection with atypical organisms, notably CMV (chorioretinitis), *Listeria* (meningitis, bacteremia), and *Cryptococcus* (meningitis). Similar data exists for infection risk in bone marrow transplant (BMT) patients.

The cornerstones for the management of infections in the immunocompromised patient are early diagnosis and appropriate treatment. The clinical approach to the potentially infected immunocompromised patient involves early assessment, careful evaluation of subtle clinical findings, aggressive diagnostic tests, early empirical broad-spectrum antimicrobial therapy, anticipation of potential complications and coinfections, monitoring of clinical response and side effects,

and, whenever possible, reduction of immunosuppression.

Patients must undergo a detailed history, physical examination, and laboratory evaluations and investigations. The resulting data are used to rapidly implement a rational empirical therapeutic regimen tailored to the probable etiological agents. The history should evaluate the nature, severity, regimen, and duration (or expected duration) of the immunosuppressed state, to provide information about the host's "net state" of immunosuppression. Similarly, in patients receiving solid organ transplant, it is helpful to identify the donor and recipient serological status for certain infections like CMV.

Localizing symptoms, if present, can narrow the field of potential pathogens. Knowledge of prior treatment can help to differentiate between therapy-induced disease and infection (eg, bleomycin or radiation-induced pulmonary fibrosis vs atypical pneumonia). Previous infections can point to the possibility of recurrence, particularly with defects of cell-mediated immunity. Prior antibiotic use can alter endogenous flora, changing the identity of probable pathogens. Use of prophylactic regimens can influence the differential diagnosis of infection in the critically ill; it can lower the likelihood of certain diagnoses (eg, *P jirovecii* infection in HIV-infected patients receiving trimethoprim-sulfamethoxazole) or increase the chance of others (eg, α-hemolytic streptococcal or resistant gram-negative bacteremia in neutropenic patients receiving ciprofloxacin or trimethoprim-sulfamethoxazole).

The physical examination should be complete and should include specific areas often underappreciated in routine examinations. A funduscopic examination may show evidence of *Candida* endophthalmitis or either *T gondii* or CMV chorioretinitis. A close neurological examination may reveal subtle findings consistent with cryptococcal meningitis or cerebral toxoplasmosis (eg, nuchal rigidity, focal deficits). The skin may show evidence of infection by certain pathogens (eg, herpetic vesicles, ecthyma gangrenosum associated with *Pseudomonas*, or lesions typical of disseminated *Candida* or *Aspergillus*) or infection of the intertriginous areas. Clinicians should inspect the patient's oral cavity, where odontogenic abscesses, *Candida* esophagitis or pharyngitis, and herpetic mucositis may exist. Patients with oral mucositis and neutropenia can present with fever and pharyngitis and develop a diffuse erythematous rash presenting as toxic shock syndrome due to viridans streptococci. Examination of the anus and surrounding tissue is necessary to rule out perirectal abscesses and cellulitis.

Laboratory investigations of specimens from the potentially infected immunocompromised patient can be extremely useful. Relatively trivial laboratory abnormalities may be indicative of significant disease.

Microbiological examination of available body fluids and tissues is key in the evaluation of the immunocompromised patient suspected of harboring infection. The selection of necessary tests and assessment of results depends on the underlying immune deficit, the clinical presentation, and the most likely cause of infection. Gram stain of all samples, cultures for typical and atypical pathogens, viral polymerase chain reaction (PCR),[14,15] and specific stains[16] should be performed. Serological testing is rarely of use for acute management but can help in the later diagnosis of various viral and fungal infections.[17,18]

The lung is the single most frequently infected organ in immunocompromised patients.[8] If sputum is obtainable, a Gram stain and routine culture and sensitivities are required, even if pulmonary symptoms are relatively minor; PCR for influenza virus should be performed during flu season. Antigen detection for *Legionella pneumophila* is indicated for both community- and hospital-acquired diseases. Neutropenic patients may exhibit marked symptoms of pulmonary origin in the absence of significant infiltrates and sputum production. In patients with cell-mediated immune deficits, special stains such as a Ziehl-Neelsen (acid fast stain) for mycobacteria (eg, *Mycobacterium tuberculosis*, *M avium-intracellulare*) or *Nocardia* and Wright-Giemsa stain for *P jirovecii* and other fungi are required. PCR techniques can be used (eg, on acid fast smear–positive specimens for species identification or on smear-negative sputum specimens); sensitivity and specificity are approximately 50% and greater than 95%, respectively, for acid fast smear–negative sputum specimens.[16] PCR can be used also to determine influenza virus and *Aspergillus* species.[14,15] Adenosine deaminase testing on lymphocytic pleural fluid can be conducted when there is a high pretest probability for tuberculosis.[19] If sputum cannot be obtained noninvasively and clinical suspicion is high (eg, chest radiograph infiltrates), bronchoscopy with bronchoalveolar lavage with or without biopsy may be indicated.

Chest radiograph (posteroanterior and lateral) is the most useful initial radiological test and is mandatory in all immunocompromised patients with a suspected infection. Other radiological investigations such as computed axial tomography, of choice when an abdominal or neurological source is suspected, or a magnetic resonance, in patients with neurological symptoms and a normal computed tomography result, can occasionally detect otherwise occult lesions or

further delineate suspected pathological processes. Nuclear imaging techniques can occasionally be useful (eg, gallium scanning for *P jirovecii* pneumonia, indium-labeled white blood cell scanning for occult abdominal abscesses). However, the immune defects of this patient group (particularly neutropenia) can limit the utility of such leukocyte-dependent studies. Newer modalities such as indium-labeled immunoglobulin G may prove of greater utility in the immunocompromised patient.

Despite the need for an aggressive search for infection in immunocompromised patients, the potential for noninfectious causes of fever due to drugs, underlying or unrelated diseases must also be considered. Among malignancies, lymphoma and hypernephroma are frequently associated with fever. Allograft rejection may be the most common cause of fever in organ transplant recipients. Antibiotics, among the myriad of medications given to the immunocompromised, are well known to cause drug fever. Postsurgical hematoma, pulmonary embolism, and myocardial infarction are other potential causes of fever in immunocompromised patients.[20]

INFECTIONS IN NEUTROPENIC PATIENTS

Most patients become neutropenic as a consequence of leukemia or the treatment of malignancy with chemotherapy and/or BMT, or occasionally due to aplastic anemia or idiosyncratic drug reactions. The American Society of Clinical Oncology has defined neutropenia as an ANC less than 1,000/μL, severe neutropenia as ANC less than 500/μL, and profound neutropenia as ANC less than 100/μL.[21] Although overt focal processes may occur, fever is the typical presenting feature in most patients with infection and profound neutropenia (ANC <100/μL). Because of the frequent absence of focal findings, neutropenic patients with fever (>38.3°C [100.9°F]) in the absence of a defined cause must be assumed to have infection.[22] When infection is identified, 85% of infections are found in the periodontium, oropharynx, lung, distal esophagus, colon, perianal area, or skin. Bacterial and fungal pathogens dominate in all patients with neutropenia regardless of its cause. Patients with neutropenia secondary to untreated leukemia-lymphoma or aplastic anemia are at increased risk of reactivation of herpes viruses resulting in severe herpes simplex virus mucositis, disseminated VZV, and CMV infection.

The dominant predictors of risk of infection during neutropenia due to chemotherapy are the degree and duration of neutropenia.[23] The risk of bacterial infection is significantly increased when the ANC falls below 500/μL. A marked

increase in risk is seen in profound neutropenia (ANC <100/μL). Neutropenia due to drug reactions, aplastic anemia, or congenital cyclic neutropenia involves a relatively isolated immune defect without mucosal injury. In contrast, cytotoxic chemotherapy impairs mucosal integrity and phagocytic function of surviving neutrophils and also affects humoral and cell-mediated immunity. When fever and infection do occur in the first few days (<1 week) of neutropenia, gram-positive cocci are frequently responsible. In patients with more prolonged neutropenia, gram-negative bacilli become problematic in the second and third weeks. After 3 weeks of neutropenia, the incidence of opportunistic fungal infections increases, particularly with *Candida* and *Aspergillus* species and more exotic pathogens such as *Mucor* species, *Trichosporon* species, and even *Fusarium* species.

Typically, infections in patients with neutropenia are due to endogenous bacteria (although half may be hospital acquired). Nosocomial acquisition may have occurred from physical contact (gram-negative rods, gram-positive cocci), water sources (*Legionella*), or air (*Aspergillus*). Potential sources of infection with endogenous organisms include skin (eg, *Staphylococcus* species, *Corynebacterium* species, *Bacillus* species, gram-negative rods, and *Candida*) and gut (eg, gram-negative rods [*Escherichia coli*, *Klebsiella* species, and *P aeruginosa*] and *Candida* species). In recent decades, organisms such as *Stenotrophomonas maltophilia* causing pneumonia, *Burkholderia cepacia* causing line sepsis, and *Aeromonas hydrophila* leading to necrotizing fasciitis, as well as *Leuconostoc* species, *Capnocytophaga* species, and *Rhodococcus equi*, have all emerged as important pathogens. This shift has occurred for a variety of reasons, including use of prophylactic antibiotics and chemotherapeutic regimens causing greater mucositis.

A number of principles, developed in the 1960s, continue to be relevant to the management of fever from an undefined source in the neutropenic host. First, empirical antibiotics should be started in the neutropenic patient (ANC <500/μL) with fever (temperature >38.5°C [101.2°F] on 1 occasion or >38°C [100.3°F] on 2 occasions) of unknown origin within an hour from developing fever, since in this population infection can progress rapidly and become life threatening. This principle is based on the observation that despite the difficulty in defining a site of infection at the time of fever onset, empirical therapy with antibiotics clearly decreases mortality during neutropenic fever.[24] Second, as a rule, broad empirical antibiotics should be used, particularly in the ICU. Third, broad-spectrum antibiotics should be continued for the duration of the neutropenia or

for 10 to 14 days if the ANC recovers to greater than 500/µL (whichever is longer). Fourth, the specific choice of the initial antibiotic regimen is dependent on the microbial flora of the local environment. This includes both sensitivity patterns of likely endogenous flora present on the individual and sensitivity patterns of pathogens known to circulate in the local nosocomial environment. Finally, if fever persists or recurs in a neutropenic patient after 4 to 7 days of broad-spectrum antibacterial therapy, empirical antifungal therapy is required.[24]

Both granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have been shown to abbreviate the duration of chemotherapy-related neutropenia and also decrease the incidence of infections in high-risk patients. These agents should be reserved for patients in whom a relatively prolonged duration of neutropenia (>10 days) is anticipated.[25,26] In contrast, various antiendotoxins and anticytokines (monoclonal antibodies, receptor antagonists) have not been shown to have utility in treating any form of clinical infection.

INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Since 1980, the success rates of solid organ transplantation have increased dramatically. This improvement has largely been due to the introduction of effective immunosuppressive compounds such as cyclosporine as well as advances in surgical technique. Immunosuppression in these patients primarily reflects iatrogenic, pharmacologically induced depression of cell-mediated immunity (cellular immune function) for purposes of graft retention. Pharmaceutical agents that induce defects of cell-mediated immunity include high-dose steroids (>60 mg/d prednisone equivalent), azathioprine, low-dose cyclophosphamide, vincristine, bleomycin, muromonab-CD3, antilymphocyte or antithymocyte globulin, and, to a lesser extent, cyclosporine and tacrolimus. The dominant causes of cell-mediated immune defects in developing nations are malnutrition and HIV infection.

The risk of infection and the most likely cause are related to the nature of the immune defect (cell-mediated immunity), the degree and duration of the postoperative immunosuppression, the period of time since the transplant, and the organ transplanted.[8,27-29] Thus, this population is at higher risk of intracellular pathogens, including most viruses.

Post transplant infections are divided into 3 major categories based on the postsurgical time period.[8,27-29] During the first period, the first month post

transplant, the majority of infections are similar to those in any postsurgical patient. In the second time period, from the second until the sixth month post transplant, opportunistic infections predominate. The third time period, 6 months or more post transplant, is characterized by infections similar to those in an immunocompetent individual. However, a continuing requirement for high-dose pharmacological immunosuppression, certain chronic herpes virus infections (CMV and EBV), or the presence of graft-vs-host disease will substantially alter these timelines.[8,13]

Most early postoperative infections in recipients of solid organ transplant are similar to those occurring in immunocompetent patients; however, the clinical course in the former group may be more severe and evolve rapidly, becoming medical emergencies. Surgical wound and IV catheter infections, urinary tract infection, and pneumonia represent typical infections of this period. Pathogens responsible for these infections are typically nosocomial in origin and will carry resistance patterns endemic to ICU organisms.[30] The majority of remaining early post transplant infections are caused by reactivation of latent or subclinical infections that were present in the recipient before transplant. Reactivation is triggered by perioperative nonspecific insults and intense immunosuppression. Typical organisms include herpes simplex virus, *M tuberculosis*, geographically restricted mycoses (*Histoplasma capsulatum* and *Coccidioides immitis*) and, occasionally, *Strongyloides stercoralis* and *T gondii*.[31] Opportunistic pathogens do not normally present in this early postoperative period since they require a prolonged period of immunosuppression to manifest.

Following the first month post transplant, defects of cellular immunity due to pharmacological intervention begin to have a greater impact on the nature of infections. The risk for infections is maximal between 1 and 6 months[13] (with serious life-threatening infections occurring 3-4 months after transplant). The immunomodulating viruses (CMV, EBV, and HIV) are among the major infectious concerns during this period. Infection with these viruses can further increase the patient's risk of developing opportunistic infections caused by *P jirovecii*, *Listeria monocytogenes*, *Aspergillus*, *Nocardia*, *T gondii*, *S stercoralis*, and *Cryptococcus* species.

The actual organ transplanted is crucial in determining the risk of infection, especially during the first 3 months. Because of surgical anastomoses, surgical denervation of the graft, and the absence of lymphatic drainage, recurrent and severe infections tend to occur in the transplanted organ. For example, lung transplant recipients tend to exhibit recurrent pneumonias, involving both

standard bacterial pathogens and opportunistic organisms. Liver transplant recipients exhibit biliary sepsis with increased frequency. Renal transplants are often complicated by recurrent urinary tract infection.

Normally, at 6 months post transplant, pharmacological immunosuppression is minimized and graft function is optimal. At this point, the origin and risk of infections for most graft recipients (75%) begin to approximate those of immunocompetent individuals. Twenty-five percent continue to have difficulties, like chronic viral infections (CMV, EBV, and hepatitis) that can lead to graft failure or malignancy. About 15% of transplant recipients will undergo chronic rejection, which necessitates sustained use of high-level pharmacological immunosuppression with the attendant increased susceptibility to developing opportunistic pathogens.

CMV infection is the most common infection-related cause of fever without a defined source in organ transplant recipients. Typically, the infection occurs through reactivation of latent virus in a seropositive transplant recipient. Seronegative recipients who receive CMV-seropositive organs carry a higher risk of clinical disease due to CMV infection, and in such cases, the clinical course of the infection may be especially severe. Without prophylactic CMV treatment, CMV disease typically occurs during the first 3 months after transplant.[32] CMV infection has been associated with graft rejection and virally induced immunosuppression beyond the first 6 months post transplant, resulting in prolonged susceptibility to other opportunistic infections.

INFECTION IN BONE MARROW TRANSPLANT RECIPIENTS

Recipients of BMT have an increased risk for a variety of infections, depending on the degree, type, and duration of immunosuppression; the exposure to microorganisms, as well as their virulence; and the presence of organ dysfunction and/or invasive devices such as central lines.

Three time periods corresponding to the nature of infectious risk have been defined for BMT recipients.[29,33-35] The first encompasses the preengraftment period, occurring from bone marrow ablation until 30 days post transplant. Infections in this period are primarily related to the severe neutropenia and mucositis caused by the cytotoxic conditioning regimen. The second time period, the postengraftment period, lasts from 30 days to 100 days post transplant. For the most part, infection risk in this period occurs as a consequence of the defect of cell-mediated immunity caused by the antirejection immunosuppressive

regimen. Since allogeneic transplants require greater immunosuppression, they tend to entail higher rates of infection than autologous transplants. Infections in this period involve pathogens similar to those seen in solid organ transplant recipients. The dominant concerns are CMV infection, *P jirovecii*, and nonspecific interstitial pneumonia. Invasive aspergillosis is also a concern in these patients, although acute and chronic graft-vs-host disease and CMV disease are more common.[36] During the third time period, the late post transplant period, beginning 100 days after transplant, VZV reactivation and viral respiratory infections become more common and are associated with a high general dissemination and mortality rate.

INFECTIONS IN PATIENTS WITH HUMORAL IMMUNE DEFECTS, ASPLENIA, OR COMPLEMENT DEFICIENCY

Defects of humoral immunity, complement deficiencies, and functional or anatomical asplenia[37-40] impair clearance of extracellular bacteria. This results in a predisposition to bacteremia and shock due to encapsulated organisms. Multiple myeloma and chronic lymphocytic leukemia are the most common causes of a dominant defect of humoral immune function.[37] Congenital deficiencies of functional complement components are rare.[37]

Pneumococcal infections including pneumonia, meningitis, and septic shock with purpura fulminans are the leading concerns in this group of patients.[38-40] Other infections of concern include *Haemophilus influenzae* (pneumonia, septic shock) and *Neisseria meningitidis* (meningitis, septic shock), *Klebsiella* (pneumonia), and *E coli* (pyelonephritis). Appropriate management requires an awareness that infections in these patients may progress rapidly into fulminant septic shock.

BIOLOGICAL AGENTS AND INFECTION

Three groups of biological interventions exist for control of systemic inflammatory diseases like rheumatoid arthritis; these biological agents work by interfering with cytokine function, inhibiting T-cell activation, and causing B-cell depletion. The first group contains the current tumor necrosis factor α (TNF-α) blocker agents (etanercept, infliximab, adalimumab, certolizumab, golimumab, and natalizumab); the interleukin 1 inhibitor anakinra; and the interleukin 6 inhibitor tocilizumab. In the second group, abatacept inhibits T-cell activation by preventing T-cell receptors from binding to costimulatory molecules. Rituximab, an anti-CD20 antibody, depletes B cells as a member of

the third group.

TNF-α inhibitors are associated with an increased risk for serious infections, with nearly a 5-fold relative increase in the rate of infections in the first 90 days after starting therapy compared with controls.[41-43] Important bacterial infections include tuberculous and nontuberculous mycobacterial infections: listeriosis, legionellosis, and nocardiosis.[44] Viral infections such as acute or chronic hepatitis B and C are contraindications to therapy with TNF-α inhibitors because of the risk of reactivation. Reactivation of VZV and CMV is also known to occur. Fungal infections due to *H capsulatum*, *C immitis*, *Aspergillus* species, and *Cryptococcus* species have been documented.[45] Rituximab has been associated with *P jirovecii* and aspergillosis.

NONSPECIFIC IMMUNODEFICIENCY STATES AND INFECTION

A number of diseases and other conditions that do not specifically impair immune function can cause immunocompromise secondarily. Each results in a predisposition to severe, potentially life-threatening infections. Such conditions include protein-calorie malnutrition, diabetes, renal failure, and hepatic failure.

A bidirectional relationship exists between nutrition and infection. A deficient nutritional state predisposes toward infection, whereas infection increases the metabolic rate and nutritional requirements. Malnutrition is both a risk factor and an aggravating factor for infection[46] and the leading cause of immunodeficiency worldwide. Although malnutrition has not been well appreciated as a cause of immunosuppression-related infections, it results in a myriad of immune function abnormalities that involve T-cell, B-cell, neutrophil, and complement function. These include thymic and lymph node atrophy, impaired T-cell–dependent B-lymphocyte responses, reductions in CD4, and impaired neutrophil chemotaxis and bactericidal activity. Malnutrition also is associated with impaired wound healing and increased wound infections. The important role of nutrition in ensuring an appropriate immune response is reflected in recent efforts to optimize the nutritional status of critically ill patients.

Diabetes is well known to be associated with increased risk of infection.[47,48] The cause is not entirely clear, although immune dysfunction is well documented.[49] Possibilities include the direct consequences of diabetic vasculopathy and/or neuropathy as well as the indirect consequences of diabetic hyperglycemia that impairs neutrophil chemotaxis, adherence, and phagocytosis.[49] Increased glucose concentration in urine and mucosal secretions leading to increased

colonization with bacteria and *Candida* species may contribute. As a consequence of these factors, diabetic patients have an increased risk for a variety of life-threatening infections including bacterial pyelonephritis, pulmonary tuberculosis, and necrotizing polymicrobial cellulitis.

Renal failure and its management are associated with defects of both specific and nonspecific elements of host defenses.[37,50] Defects of nonspecific defenses include vascular and peritoneal access devices for dialysis. Specific immune defense elements are impaired by exposure of blood to hemodialysis membranes (complement depletion, leukocyte dysfunction) and by the direct effects of uremia, which causes cellular immune deficits (thymic atrophy, lymphopenia, decreased interferon production, and impaired delayed hypersensitivity responses). Splenic clearance of opsonized and nonopsonized pathogens appears to be defective, as do neutrophil chemotaxis and phagocytosis. The result is a propensity to infections associated with breaches of integumentary barriers (IV catheter–related infections, peritonitis in peritoneal dialysis patients, urinary tract infection, wound infections) and with specific immune deficits (*P jirovecii* pneumonia, esophageal candidiasis, chronic viral hepatitis, bacterial pneumonia, and bacteremia). Infection is the leading cause of death (30%-70%) in patients with acute renal failure.

Hepatic failure and end-stage cirrhosis represent an immunocompromised state.[37,51] Serious infections develop in as many as 80% of patients with fulminant hepatic failure. At least 3 factors place such patients at increased risk of infection. First, in hepatic failure, the Kupffer cells of the liver fail to clear the many enteric bacteria normally found in the portal venous flow, resulting in systemic bacteremia. Second, the liver synthesizes 90% of the complement components and is the major organ through which opsonized pathogens (primarily bacteria) are removed. Third, patients with fulminant hepatic failure and end-stage cirrhosis require supportive care (endotracheal intubation, intravascular devices, urinary catheterization) that breaches normal mucocutaneous barriers, which places the patient at significant risk for a variety of infections.

The association between blood transfusions and immunosuppression has been recognized for at least 30 years.[52] The degree of immunosuppression was such that a single blood transfusion prior to cadaveric kidney transplant reportedly improved graft survival as long as 5 years post transplant.[53] This phenomenon of immunosuppression resulted in prospective, randomized controlled trials to assess the impact of blood transfusions on postoperative infection rates and

survival.[54] The heterogeneity of study methods and wide range of study results have limited the ability to draw definitive conclusions.[55] Transfusion-induced immunosuppression is believed to be mediated by passive transfusion of allogeneic white blood cells.[55] Impaired NK cell and macrophage function as well as defective antigen presentation have been shown to occur.[56] Concerns over the adverse effects of blood transfusions have led many centers to adopt universal leukoreduction of white blood cells in blood transfusions. The clinical efficacy of this approach in reducing risk of infection remains to be seen.[54]

SUMMARY

Immunocompromised patients are vulnerable to an exceptionally broad variety of infections including those caused by acquired opportunistic pathogens, reactivation of latent organisms, and typical community or nosocomial pathogens. The most likely pathogens at any given point are predictable in immunocompromised patients. Keys to determining probable causes of infection include knowledge of the nature of the immune defect (humoral, cell mediated, neutrophil) and the duration and severity of the defect. Profoundly neutropenic patients (<100 PMNs/μL) are prone to bacterial and fungal infections within the first weeks of severe neutropenia; recovery typically ensues as PMNs increase to more than 500/μL. In recipients of solid organ transplant, standard perioperative infections are common during the early perioperative period, with opportunistic pathogens dominating between the first and sixth months; successful engraftment is associated with a relatively normal infection profile after 6 months. In BMT recipients, bacterial and fungal neutropenia-associated infections are common during the first 20 to 30 days, whereas CMV and *P jirovecii* pneumonia dominate from 30 to 100 days post transplant; VZV and viral respiratory infections are problematic after 100 days. Humoral or complement defects and asplenia predispose to bacterial infections and septic shock, particularly with encapsulated organisms. Early assessment, careful evaluation of subtle clinical findings, aggressive diagnostic testing (including invasive procedures where necessary), rapid administration of empirical broad-spectrum antimicrobial therapy, and reduction of immunosuppression where possible are key to the successful management of infections in the immunocompromised patient.

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CHAPTER 28

Specific Infections With Implications for Critical Care

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Key words: severe community-acquired pneumonia, community-acquired pneumonia, methicillin-resistant *Staphylococcus aureus*, intra-abdominal infections, *Clostridium difficile*, necrotizing soft tissue infections, meningitis, encephalitis

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is the most common cause of infection-related hospitalizations and mortality. A recent population-based study reported that the annual incidence of CAP was 25 cases per 10,000 US adults. More than 20% of these patients required intensive care. Patients with severe community-acquired pneumonia (SCAP), operationally defined by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) as patients requiring ICU admission, are at higher risk of mortality (36.5%).

Multiple organisms give rise to CAP (**Table 1**). The most commonly occurring bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Chlamydophila pneumoniae.* SCAP develops if the causative pathogen is virulent or the host is sufficiently compromised. The causes of SCAP are somewhat different from the causes of less severe CAP, and a greater proportion of SCAP patients are affected by gram-negative bacteria, *Legionella*, and *Staphylococcus aureus* including methicillin-resistant *S aureus*

(MRSA). *S pneumoniae*, however, remains the most common bacterial cause of SCAP. Most patients with SCAP (45%-65%) have associated risk factors (**Table 2**).

Table 1. Microbiological Causes of Community-Acquired Pneumonia (CAP)

CAP	CAP Requiring Hospitalization	Severe CAP
Streptococcus pneumoniae	*S pneumoniae*	*S pneumoniae*
Mycoplasma pneumoniae	*Legionella* species	*Legionella* species
Chlamydophila pneumoniae	*C pneumoniae*	*Staphylococcus aureus*, including methicillin-resistant *S aureus*
Respiratory viruses[a]	*M pneumoniae*	Gram-negative organisms, including *Pseudomonas aeruginosa*
	Respiratory viruses[a]	Respiratory viruses[a]

[a]Human rhinovirus, influenza A and B, human metapneumovirus, respiratory syncytial virus, parainfluenza, coronavirus, adenovirus.

Table 2. Risk Factors for Developing Severe Community-Acquired Pneumonia

Advanced age (older than 65 y)
Comorbid illness, such as chronic respiratory illness (including chronic obstructive pulmonary disease), cardiovascular disease, diabetes mellitus, neurological illness, renal insufficiency, and malignancy
Cigarette smoking (risk for pneumococcal bacteria)
Alcohol abuse
Absence of antibiotic therapy prior to hospitalization
Failure to contain infection to its initial site of entry
Immune suppression
Genetic polymorphisms in the immune response

In recent years, highly sensitive molecular diagnostic testing has identified an increasing number of viral pathogens previously not considered to typically cause severe pneumonia among immunocompetent adults. Several studies suggest that roughly 15% of hospitalized patients with CAP have viral pneumonia and nearly 50% of patients with SCAP have either isolated viral or concomitant viral-bacterial pneumonia. These results, however, are subject to significant variation based on seasonality, type of molecular method selected, and method for obtaining samples. Significant viral pathogens are listed in **Table**

1.

Pathogenesis

Organisms that commonly colonize patients with host defense impairments can cause pneumonia. Pneumonia can also occur in patients who have an adequate immune system if the bacterial inoculum is sufficiently large or the organism is virulent. The most common route of inoculation is via the oropharynx. Very rarely, CAP occurs secondarily from a distant source through bacteremia as in *Fusobacterium necrophorum* (Lemierre syndrome) or *S aureus* and right-sided endocarditis.

Criteria for ICU Admission

Timely recognition of severe illness and provision of intensive care are crucial factors that affect survival. Some 10% to 20% of patients with CAP will require admission to the ICU, and data from large registries suggest that delayed admission to ICU dramatically reduces survival. Therefore, initial severity scoring and appropriate triage of patients at risk of poor outcome are critical. Absolute criteria for ICU admission include ventilator and vasopressor support. Several severity scores based on quantifiable objective data have been proposed but not prospectively evaluated, including the CURB 65 (**Table 3**) and ATS (**Table 4**) criteria.

Table 3. CURB 65 Scoring System[a]

Confusion (new-onset) regarding person, place, or time
Uremia, blood urea nitrogen level >20 mg/dL
Respiration rate ≥30/min
Blood pressure <90 mm Hg (systolic)
Age >**65** y

[a]1 point is assigned for each characteristic. Scores of 3 to 5 are associated with increased risk of death.

Information taken from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-72. Ewig S, Birkner N, Strauss R, et al. New perspectives on community-acquired pneumonia in 388,406 patients: results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax*. 2009;64:1062-1069.

Table 4. American Thoracic Society/Infectious Diseases Society of America Criteria for Severe

Community-Acquired Pneumonia[a]

Minor Criteria	
	Respiratory rate ≥30 breaths/min
	PaO_2:FIO_2 ratio ≤250
	Multilobar infiltrates
	Confusion, disorientation
	Blood urea nitrogen level ≥20 mg/dL
	White blood cell count ≤4,000/μL
	Platelets <100,000/μL
	Core temperature <36°C (96.7°F)
	Hypotension requiring aggressive fluid resuscitation
Major Criteria	
	Invasive mechanical ventilation
	Need for vasopressors

[a]Requirement for noninvasive ventilation can substitute for respiratory rate or PaO_2:FIO_2 ratio. ICU admission suggested if 3 or more minor criteria are met.

Diagnostic Tests

The diagnostic testing recommended for patients with SCAP is delineated in **Table 5**. Pulmonary secretions for Gram stain and culture should be obtained from either bronchoalveolar lavage or endotracheal aspirate. Blood cultures, positive in 4% to 17% of patients, are recommended prior to initiation of antibiotics. Although not necessarily predictive of increased mortality, positive blood cultures are highly specific and help to narrow the spectrum of antibiotic therapy. Atypical CAP can show few or no organisms on Gram stain. Molecular methods to detect respiratory viruses are increasingly available and can be performed on both nasopharyngeal and bronchoalveolar lavage specimens.

Table 5. Recommended Diagnostic Tests in Severe Community-Acquired Pneumonia

Blood cultures (prior to antibiotics)
Sputum or endotracheal aspirate or bronchoalveolar lavage
Gram stain
Routine bacterial cultures
Legionella culture
Viral cultures or molecular methods (polymerase chain reaction)
Legionella urine antigen
Streptococcus urine antigen
Special circumstances (immunosuppression, organ transplantation, tumor necrosis factor

inhibitor therapies, HIV, AIDS)

Silver stains for *Pneumocystis carinii* pneumonia

Fungal cultures and smears

Acid-fast bacillus smears and cultures

Currently available urinary antigen testing can be helpful in identifying the causative pathogen. *Legionella* urine antigen is recommended. This test is 70% to 90% sensitive and nearly 100% specific for *Legionella pneumophila* serogroup 1 only, which causes the majority (80%) of severe *Legionella* infections. A urine antigen for *S pneumoniae* is approximately 50% to 80% sensitive and more than 90% specific for pneumococcal pneumonia.

Other tests, including acid-fast bacillus (*Mycobacterium tuberculosis*) smear and culture and fungal stains and cultures for endemic fungi such as *Histoplasmosis capsulatum* and *Coccidioides immitis*, are indicated given appropriate geographic exposure or risk. Cytological testing with silver stain or fungal stains should be performed when *Pneumocystis jiroveci* is suspected. Pleural fluid should be sampled in the presence of a significant parapneumonic effusion (>5 cm height). This may provide diagnostic material for culture and also exclude empyema that requires prompt adequate drainage.

All patients suspected of having CAP should undergo chest radiography. Early presentations may reveal a normal chest radiograph. Viral pneumonias typically display few or no infiltrates, whereas bacterial pneumonias often have focal segmental or lobar distribution. However, atypical pathogens can present with a pattern mimicking a typical pathogen.

Specific Pathogens

Gram-Negative Pneumonia

Pseudomonal infection is most commonly seen in patients with structural lung disease including cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease treated with frequent steroids and outpatient antibiotics. The primary risk factor for other nonpseudomonal gram-negative pneumonias (*Klebsiella* species and *Acinetobacter* species) is alcohol abuse. A Gram stain of sputum, a tracheal aspirate, or a lavage specimen will show many polymorphonuclear leukocytes and gram-negative bacilli indicating the necessity for gram-negative coverage. The requirement for double drug coverage of

Pseudomonas is unproven. Patients who receive adequate initial therapy show a trend toward improved survival. This observation has driven the recommendation for double-drug treatment of presumed or suspected *Pseudomonas* pneumonia.

Staphylococcus aureus

S aureus, including MRSA, causes CAP in patients who have had influenza infection, patients receiving dialysis, elderly patients who have comorbid diseases or reside in long-term healthcare facilities, and patients recently hospitalized. Recently, MRSA lung infections have been seen in young, previously healthy adults with rapidly progressive necrotizing pneumonia frequently associated with cavitation. Sputum Gram stains, tracheal aspirates, or lavage specimens will show polymorphonuclear leukocytes and gram-positive cocci in clusters. Extensive tissue destruction has been linked to the expression of staphylococcal exotoxins, which can be associated with both methicillin-sensitive *S aureus* (MSSA) and MRSA.

Legionella Species

Legionella infection is frequently severe and highly associated with SCAP that requires ICU admission. In part this may be due to predisposing underlying diseases. The primary risk factor is exposure to infected aerosolized fresh water sources. Travel is an underappreciated risk factor (infected hotel water supplies). A careful travel history should be sought when evaluating patients with SCAP. There are no characteristic clinical findings. Since the cell wall of the organism does not stain routinely and *Legionella* is an intracellular parasite of macrophages, a tracheal aspirate may show many polymorphonuclear leukocytes but no organisms on Gram stain. Culture of respiratory secretions and urinary antigen detection are the diagnostic tests of choice, although urine antigen detects only *L pneumophila* serogroup 1, the dominant cause of severe disease. Treatment is a macrolide or fluoroquinolone, with the latter the preferred agent. Rifampin is no longer recommended in the treatment of *Legionella* pneumonia.

MULTIDRUG-RESISTANT ORGANISMS

Over the past few years, gram-positive bacterial resistance, such as in MRSA, has increased worldwide, including in the United States, where its prevalence is more than 50%. Also, the emergence of multidrug-resistant gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and

extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, has complicated the treatment of healthcare-associated infections.

Extended-Spectrum β-Lactamases

ESBL organisms were first isolated in Germany in 1983, and the first ESBL-producing isolates in the United States were reported in 1989. ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* have become increasingly common in recent years. Carbapenems tend to remain stable to the hydrolytic effects of ESBLs and hence remain an important drug of choice in their treatment. However, carbapenemase-producing Enterobacteriaceae, specifically *K pneumoniae* carbapenemases, are becoming increasingly common, limiting treatment modalities. Recommended definitive treatment for carbapenemase-producing Enterobacteriaceae is limited to colistin and tigecycline.

Since the mid-1980s, a rapid emergence in drug-resistant *A baumannii*, especially in healthcare-associated pneumonia and ventilator-associated pneumonia, has been noted. These isolates are resistant to all available antibiotics including carbapenems and polymyxins. Carbapenem-resistant *P aeruginosa* is treated with colistin. Ampicillin-sulbactam, tigecycline, and colistin remain viable options for the treatment of resistant *A baumannii*. Possible alternatives include extended infusions of carbapenems or combination therapy with rifampin, minocycline, doxycycline, or azithromycin. For pneumonia caused by these organisms, nebulized colistimethate sodium or nebulized aminoglycosides may be used.

Initial Antibiotic Treatment

Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues, revolve around the initial assessment of severity. Initiation of empirical therapy for SCAP is based on the most likely etiological pathogens in a given patient and the clinical scenario. *Legionella* species and *S pneumoniae* must be adequately addressed initially. Some important points are as follows:

1. Early initiation of appropriate antibiotic therapy is associated with improved mortality; therefore, treatment regimens must be active against the most commonly associated pathogens.

2. Monotherapy should not be used for an ICU-admitted CAP patient or any

patient with severe pneumonia.

3. Patients with shock and suspected or documented bacteremic pneumococcal disease should receive combination antibiotic treatment given the improved mortality rates.

Recommended therapy for SCAP in the absence of pseudomonal risk factors entails a selected IV β-lactam (eg, cefotaxime, ceftriaxone, ertapenem, or a β-lactam–β-lactamase inhibitor combination) combined with either a macrolide or an IV antipneumococcal quinolone (levofloxacin or moxifloxacin) (**Table 6**).

Table 6. Adult ICU Treatment of Severe Community-Acquired Pneumonia (SCAP)

Routine SCAP	Gram-Negative SCAP	SCAP Due to Methicillin-Resistant *Staphylococcus aureus*
β-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus either azithromycin or respiratory fluoroquinolone.[a] If penicillin allergy, aztreonam and respiratory fluoroquinolone recommended.	Antipseudomonal β-lactam[b] plus ciprofloxacin or levofloxacin. Alternatively, antipseudomonal β-lactam, aminoglycoside plus azithromycin (or respiratory fluoroquinolone). If penicillin allergy, aztreonam is substituted for the β-lactam.	Vancomycin or linezolid should be added. Daptomycin not to be used in pulmonary infections.

[a]Levofloxacin, moxifloxacin, or gemifloxacin.

[b]Cefepime, piperacillin-tazobactam, meropenem, or imipenem.

For patients with risk factors for *Pseudomonas* pneumonia (see below), therapy can entail a 2-drug regimen using an antipseudomonal β-lactam (imipenem, piperacillin-tazobactam, cefepime) plus ciprofloxacin or levofloxacin (750 mg daily). An alternative is a 3-drug regimen using an antipseudomonal β-lactam plus an aminoglycoside, plus either an IV antipneumococcal quinolone (levofloxacin or moxifloxacin) or a macrolide. For the truly penicillin-allergic patients (anaphylaxis to either penicillin or a cephalosporin) requiring gram-negative coverage, aztreonam is recommended in lieu of cephalosporins, synthetic penicillins, or carbapenems.

If MRSA is a concern, vancomycin or linezolid should be added. The clinical superiority of either agent has not been proven.

Timing and Duration of Treatment

Earlier antibiotic treatment in severe infection improves mortality. In the treatment of pneumonia, administration of antibiotics within 4 hours of presentation is currently considered optimal although is not associated with uniformly improved mortality or even reduced length of stay. Patients should receive their first doses of antibiotics in the emergency ward.

Duration of antibiotic therapy has not been subjected to careful clinical trials. There is general agreement that 5 days of treatment is usually sufficient in the patient whose clinical response is rapid and who meets criteria for clinical stability (**Table 7**). Patients with multilobar disease, multiple comorbid conditions, *Legionella* infection, and ICU admission (high CURB 65 scores) generally respond more slowly, and longer courses of treatment may be necessary. Transition to oral treatment is considered an indication for discharge with no need for further hospital observation. Gram-negative pneumonia (especially *Pseudomonas*), *Legionella* species, and *S aureus* may require longer courses of treatment, especially in the presence of necrosis (abscess or cavitation), although no studies have definitively confirmed this. An infected pleural space (positive Gram stain or positive pleural fluid culture) will require several weeks of antibiotic treatment in addition to adequate drainage.

Table 7. Criteria for Clinical Stability

Temperature ≤37.8°C (100°F)
Heart rate ≤100 beats/min
Respiratory rate ≤24 breaths/min
Systolic blood pressure ≥90 mm Hg
Arterial oxygen saturation ≥90% or PO_2 ≥60 mm Hg on room air
Ability to maintain oral intake
Normal mental status

Information taken from Mandell LA, Wunderink RG, Anzueto A, et al. Infectious diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-72. Menendez R, Torres A, Rodrıguez de Castro F, et al. Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. *Clin Infect Dis*. 2004;39:1783–90.

INTRA-ABDOMINAL INFECTIONS

Intra-abdominal infections are the second most common cause of infectious mortality in the ICU. They are often the most difficult infections to diagnose early and treat effectively. Mortality rate ranges from 3.5% in patients with early infection following penetrating abdominal trauma to more than 60% in patients with peritonitis and multiple-organ failure.

Intra-abdominal infections in the hospitalized patient differ from those arising in the community in their clinical presentations, sites of involvement, and microbiological characteristics. Intra-abdominal infection comprises a heterogeneous group of conditions ranging from relatively benign processes such as *Helicobacter pylori*, food poisoning and diarrhea, or pelvic inflammatory disease to conditions such as infected pancreatic necrosis, diffuse peritonitis, and intestinal infarction.

Peritonitis is defined as inflammation of the inner lining of the abdominal cavity and its organs. Primary peritonitis usually involves hematogenous seeding of ascitic fluid from bacteremia in patients with conditions such as cirrhosis, nephrosis, systemic lupus erythematosus, and peritoneal dialysis. Usually, a sole or dominant organism is responsible, and no focal disease is present. The typical flora spectrum is 5% anaerobes, 20% gram-positive organisms, and 70% gram-negative organisms. Secondary peritonitis usually results from visceral organ disease or perforation or from trauma, or it is postsurgical in nature. Most cases are polymicrobial. Tertiary peritonitis is described as continued or recurrent inflammation after initial appropriate therapy (**Table 8**).

Table 8. Primary and Secondary Peritonitis

Primary	**Secondary**
From bloodstream (spontaneous bacterial peritonitis) Usually monomicrobial Criteria for diagnosis: • Neutrophil count of 250/μL • Positive fluid culture • Low pH • Gram stain—33% sensitive	From perforation of gastrointestinal tract, intestinal necrosis, postoperative peritonitis secondary to anastomotic leak, blunt trauma, and rupture of a viscus. Polymicrobial (mixed gram-positive and gram-negative organisms indicate intestinal perforation).

Medical Treatment

Antibiotic therapy to cover gram-negative bacillary organisms and anaerobes

should be initiated. Common organisms include *E coli*, streptococci, enterococci, *Klebsiella*, staphylococci (continuous ambulatory peritoneal dialysis patients), *P aeruginosa*, and *Bacteroides* species.

Empirical Therapy

Empirical therapy consists of one of the following: a) a third- or fourth-generation cephalosporin combined with metronidazole or b) monotherapy with a β-lactam–β-lactamase inhibitor combination or a carbapenem. Nonbacteremic patients are treated for 7 to 10 days and bacteremic patients for 14 days. If source control is achieved, 4 days of treatment is sufficient.

Surgical Treatment

Patients with diffuse peritonitis should undergo an emergency surgical procedure as soon as possible, even if ongoing measures to restore physiological stability need to be continued during the procedure. In severe abdominal sepsis, delays in operative management may lead to a significantly higher need for reoperations and worse overall outcomes.

The goals of operative treatment of peritonitis are to eliminate the source of contamination, thus reducing the bacterial inoculum, and to prevent recurrent or persistent sepsis.

Hemodynamic instability may occur at any time during treatment because of bacteremia and cytokine release. Significant third spacing can occur; therefore, edema of the bowel, retroperitoneum, and abdominal wall may preclude safe abdominal closure after prolonged cases in patients who are severely ill. The development of abdominal compartment syndrome can occur with increasing bowel edema from ongoing infections, resuscitation, or both. Monitoring of a closed abdomen in this setting should include bladder pressures, typically less than 25 mm Hg, to maintain mucosal perfusion.

Intra-abdominal Abscess

Intra-abdominal abscess can result from intestinal perforation, complicated acute cholecystitis, suppurative cholangitis, acute appendicitis, diverticulitis, intestinal malignancy, or surgical procedures for trauma, ischemia, obstruction, or genitourinary infections.

Treatment

An intra-abdominal abscess can be drained via a percutaneous approach, sometimes with catheter placement, or via laparoscopy or an open operative procedure. Drains should remain in place until drainage volume is minimal. Indications for surgical drainage are failure of medical management and inability to perform drainage with a percutaneous approach (ie, peritonitis, multiple loop abscesses, source control). Antibiotic coverage should include aerobic and anaerobic microbial coverage. Repeat computed tomography can be performed to assess adequacy of drainage.

For some patients, the placement of a drainage catheter is not appropriate, and laparotomy is the procedure of choice. If clinical evaluation suggests peritonitis, the patient should proceed to surgery even if imaging demonstrates drainable collections, except in extreme circumstances when the patient is unfit for surgery.

Biliary Tract Infections

Biliary tract infections are typically polymicrobial, with gram-negative organisms and anaerobes predominating. In the progressing seriously ill patient, often the cause of infection is common bile duct obstruction or manipulation. In the established critically ill patient, acalculous cholecystitis should be considered. The source of bacteria is presumed to be the duodenum. Many antibiotics achieve therapeutic levels in the bile in the absence of obstruction but otherwise are inadequate as sole therapy.

Treatment

Antimicrobials for gram-negative bacteria with anaerobic and enterococcal activity should be instituted (**Table 9**).

Table 9. Acute Acalculous Cholecystitis and Cholangitis

	Risks	Symptoms	Workup	Treatment
Acute acalculous cholecystitis	Debilitated, hospitalized, major surgical procedure, prolonged ICU stays, hyperalimentation, bile stasis, cholecystoparesis, or gallbladder ischemia	Fever, leukocytosis, elevated liver enzymes, abdominal pain	Ultrasonography, HIDA scan, or CT scan	Open or laparoscopic cholecystectomy, percutaneous cholecystostomy for unstable patients, broad-spectrum antibiotics
Acute	Biliary stones, ductal	Fever,	Ultrasound,	Biliary

cholangitis	obstruction, or biliary stricture resulting in subsequent infection	leukocytes, elevated liver enzymes, abdominal pain	HIDA scan, or CT scan blood cultures	decompression accomplished either (a) with endoscopic sphincterotomy or percutaneous transhepatic biliary drainage procedure or (b) by surgical decompression

Abbreviations: CT, computed tomography; HIDA, hepatobiliary iminodiacetic acid.

Clostridium difficile Colitis

The primary pathogen responsible for *C difficile* colitis is a gram-positive, anaerobic, spore-forming bacillus. This type of colitis results from the loss of normal bacterial flora of the colon from antibiotic therapy. The pathogen releases toxins that cause mucosal inflammation and damage.

The spectrum of disease ranges from asymptomatic carriage to a fulminant, relapsing, or life-threatening colitis. Asymptomatic colonization with *C difficile* is 7% to 26% in acute care facilities and 20% to 50% in facilities where *C difficile* colitis is endemic. Colonization occurs by the fecal-oral route. The spores are heat-resistant and can persist in the environment for months. Normal gut flora can resist *C difficile* colonization, but antibiotic use suppresses the normal flora, which allows growth of *C difficile.*

C difficile colitis should be suspected in any patient with diarrhea who has received antibiotics recently or when diarrhea occurs persistently during hospitalization.

Common antibiotics implicated in *C difficile* colitis include cephalosporins (especially second- and third-generation), ampicillin-amoxicillin, and clindamycin. Other types of antibiotics that have been associated with *C difficile* colitis are the macrolides (ie, erythromycin, clarithromycin, azithromycin) and other penicillins.

Risk Factors

Risk factors include antimicrobial use (longer duration and multiple agents), chemotherapy agents, advanced age, number of comorbidities, underlying disease severity, duration of hospitalization, exposure to other patients with *C difficile* colitis, and acid-suppressing medications.

Genetic polymorphisms in toxins A (enterotoxin) and B (cytotoxin) and the emergence of the highly virulent B1/NAP/027 strain have resulted in an increase in the disease severity. Criteria commonly associated with severe *C difficile* infection include the following:

1. Age older than 60 years
2. White blood cell (WBC) count >20,000/µL or <4,000/µL or >10% bands
3. Serum albumin level <2.5 g/dL
4. Serum creatinine level >2 mg/dL or increase in creatinine by 1.5 mg/dL from baseline
5. Evidence of small bowel obstruction, paralytic ileus, or toxic megacolon
6. Cardiorespiratory failure (intubation or vasopressors)
7. Endoscopic evidence of pseudomembranous colitis
8. Lactate level ≥5 mmol/L
9. Altered mental status
10. Immunosuppression

Symptoms

Symptoms include fever, cramping abdominal pain, mucus or occult blood in the stool, diarrhea (may be self-limiting), and peripheral leukocytosis (50% of the time). Rarely, cases of arthritis or bacteremia, ileitis, or pouchitis are noted in patients with previously performed total colectomy. The symptoms range from mild to fulminant.

Diagnosis

Enzyme immunoassay detecting the presence of toxins A and B, and polymerase chain reaction (PCR) are methods most often used for diagnosis. Sensitivity of enzyme immunoassay is high (95%-99%); however, specificity is only moderate with significant variability (65%-95%). PCR has high sensitivity and specificity at 97% and 93%, respectively. Colonoscopic examination may reveal pseudomembranes, but risk of bowel perforation can be significant. PCR detection of *C difficile* does not differentiate between asymptomatic and active

infection.

Complications

Complications of *C difficile* colitis comprise dehydration, electrolyte disturbances, hypoalbuminemia, toxic megacolon, bowel perforation, hypotension, renal failure, systemic inflammatory response syndrome, sepsis, and *C difficile* colitis can result in death.

Treatment

A positive toxin assay result in a patient with minimal or no symptoms should not prompt treatment. For initial episodes with mild to moderate severity, leukocytosis of 15,000 cells/µL or lower, and a serum creatinine level less than 1.5 times the premorbid level, the recommended treatment is metronidazole (500 mg 3 times per day by mouth) for 10 to 14 days.

For severe, initial episodes that entail leukocytosis with a WBC count of 15,000/µL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level, vancomycin (125 mg 4 times per day by mouth) is administered for 10 to 14 days.

For severe, complicated initial episodes that constitute hypotension or shock, ileus, or megacolon, the recommended treatment is vancomycin (500 mg 4 times per day by mouth or by nasogastric tube) plus metronidazole (500 mg every 8 hours IV). If complete ileus is present, the addition of rectal instillation of vancomycin should be considered.

Total colectomy with rectal preservation should be considered in fulminant, life-threatening *C difficile* colitis with increasing lactate level and WBC count or if the patient does not respond to medical treatment. Very high lactate, pressor dependence, and WBC count increase postoperative mortality. Hence, colectomy should be performed as early as possible, especially in patients with toxic megacolon, colonic perforation, severe ileus, acute abdomen, diffuse peritonitis, and septic shock. Colectomy appears to be more beneficial in patients aged 65 years or older, patients who are immunocompetent, patients with leukocytosis (WBC count ≥20,000/µL), or patients with lactate levels less than 5 mmol/L.

Relapses

Approximately 20% of patients treated for *C difficile* colitis will have a

recurrence. With each relapse, the chance of a subsequent episode of *C difficile* colitis markedly increases—to about 40% after a first recurrence and to more than 60% after 2 or more recurrences. The treatment of the first recurrence is the same as for the initial occurrence of *C difficile* colitis. With the second recurrence, the suggested dosing of oral vancomycin is 125 mg 4 times a day for 14 days, 2 times a day for 7 days, once a day for 7 days, once every 2 days for 8 days, and once every 3 days for 15 days. For a third recurrence, the suggested regimen includes vancomycin, 125 mg 4 times a day for 14 days, followed by rifaximin at a dose of 400 mg twice daily for 14 days.

Two randomized controlled trials demonstrated that fidaxomicin is noninferior to vancomycin in the initial treatment of *C difficile.* Fidaxomicin, however, achieved a greater than 50% relative reduction in recurrence of disease at 28 days compared with vancomycin, results that some authorities suggest could offset the very high acquisition costs of fidaxomicin.

A recent randomized controlled trial showed that fecal microbiota transplant, usually administered either through a nasogastric tube or at colonoscopy, was highly effective in treating multiply recurrent *C difficile* infections. Alternate therapies such as probiotics (*Lactobacillus* species and *Saccharomyces boulardii*), IV immunoglobulins, and anion exchange resins such as cholestyramine and tolevamer have little proven role in the treatment of critically ill patients.

NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections (NSTIs) are a spectrum of disease involving skin, subcutaneous tissue, fascial tissue, and muscle. These infections are often associated with rapid, fulminant course and high mortality. A mortality rate of 24% to 34% has been published. Making the correct diagnosis is often a challenge in these patients, who require prompt initiation of antimicrobials as well as timely surgical intervention.

Classification based on type of organism involved has been championed and involves 3 types (**Table 10**). Type I is the most common NSTI, and more than 80% of infections are in this group. These are polymicrobial infections with 4 or more aerobic and anaerobic bacteria. Both gram-positive and gram-negative organisms are responsible. Patients with underlying diseases that affect the immune system are often more susceptible. Patients with diabetes mellitus, obesity, peripheral vascular disease, chronic kidney disease, advanced age,

surgical wounds, and alcohol or drug abuse are commonly found in this group. The classic example of type I NSTI is Fournier's gangrene or necrotizing infection of the perineum.

Table 10. Summary of Types of Necrotizing Soft Tissue Infections

Type I	Type II	Type III	Other
Polymicrobial (4 or more)—mixed aerobic and anaerobic. *S aureus, Streptococcus, Enterococcus*, gram-negative rods, *Bacteroides,* and *Peptostreptococcus*	β-hemolytic *Streptococcus* mostly, plus *S aureus* (including MRSA)	*Clostridium*	*Vibrio* and *Aeromonas*
80% of NSTI	15%	Rare	
Presence of underlying immune system compromise such as diabetes mellitus, obesity, peripheral vascular disease, chronic kidney disease and alcohol abuse is often found.	Classically young, healthy patients, often a history of trauma		Exposure to warm sea water *(Vibrio)* or fresh water *(Aeromonas)*. Liver disease a risk factor, especially chronic hepatitis B Rapid, often fatal course with cardiovascular collapse before skin findings

Type II is monomicrobial, usually associated with group A β-hemolytic *Streptococcus*, with some increasing incidence of community-acquired MRSA. Type II is often found in young, healthy patients with a history of trauma, especially involving the extremities. Almost half the cases are associated with toxic shock syndrome.

Clostridium myonecrosis is an archetypal case of type III NSTI. Its hallmark rapid progression is due to blunted host response and a myriad of potent hemolytic and proteolytic toxins. Some authors classify water-source NSTIs caused by *Vibrio* and *Aeromonas* species as type III, while other authors identify these NSTIs separately to denote their extremely aggressive course. These organisms can cause circulatory collapse prior to any soft tissue findings and should be considered in patients with a history of salt or fresh water exposure and underlying hepatic disease.

The disease process begins with microbial inoculum of the subcutaneous tissue. Endotoxins and exotoxins are produced, which cause tissue ischemia, liquefactive necrosis, and systemic toxicity by stimulating host release of cytokines. The micro-environment of ischemia that is created hinders oxidative destruction of the bacteria by neutrophils and impedes delivery of antimicrobials. Surgical debridement thereby is the mainstay of treatment for NSTI.

Diagnosis of NSTI can be difficult and most often is made clinically. Patients often have nonspecific presentation, varying time to fulminant course, and relative infrequency, which require a high index of suspicion of the diagnosis. Erythema, tenderness, and swelling are the common signs associated with the condition. Although pain out of proportion to skin findings is classic, advanced tissue necrosis may entail little or no pain. Crepitus or skin necrosis is reported in less than 20% of patients with NSTI and when present is often a late finding. Confusion with other nonsurgical conditions such as cellulitis can lead to delay in surgical debridement, which adversely affects mortality. Imaging such as plain radiography and computed tomography is helpful if gas is present. Subcutaneous emphysema in a suspicious clinical setting is pathognomonic of NSTI. However, only about a third of patients have this finding. Magnetic resonance imaging with gadolinium contrast can be helpful in distinguishing NSTI from nonnecrotizing tissue infections; however, the logistics of obtaining a magnetic resonance image for an unstable critically ill patient may delay appropriate treatment.

Treatment for NSTI is multifaceted, including surgical debridement, fluid resuscitation, broad-spectrum antimicrobial therapy, and supportive care. Expedient surgery for exploration, diagnosis, and debridement is paramount. Adequate surgical debridement of necrotic tissue is the cornerstone of therapy and should not be delayed for resuscitation or antimicrobial therapy, which can be continued in the operating room.

Broad-spectrum antimicrobial therapy should be started as soon as the diagnosis is suspected. Dosing within 1 hour should be the goal. **Table 11** shows suggested regimens for each type of NSTI. However, initial antimicrobial choice in a critically ill NSTI patient prior to Gram stain or culture should include gram-negative, anaerobic, and resistant gram-positive coverage. Clindamycin is often included in the initial regimen as it has been shown to inhibit endotoxin synthesis.

Table 11. Suggested Antimicrobial Regimen by Type

Type I	Type II	Type III	Other
Polymicrobial (4 or more)—mixed aerobic and anaerobic. *S aureus, Streptococcal, Enterococcal,* gram-negative rods, *Bacteroides,* and *Peptostreptococcus*	β-hemolytic *Streptococcus* mostly, plus *S aureus* (including MRSA)	*Clostridium*	*Vibrio* and *Aeromonas*
Piperacillin/tazobactam + clindamycin + ciprofloxacin or meropenem or imipenem/cilastin	Clindamycin + penicillin or linezolid, vancomycin, daptomycin if MRSA suspected	Clindamycin + penicillin	Doxycycline
	Clindamycin inhibits endotoxin synthesis IV immunoglobulin may be considered	Clindamycin inhibits endotoxin synthesis	

Use of adjuvant IV immunoglobulin in type II NSTI has been shown to have potential benefit based on decreasing the circulating streptococcal toxin effects and reducing toxin-induced tissue injury. Hyperbaric oxygen has been shown to inhibit infection and toxin production by *Clostridium* species. However, clinical results are mixed, and no clear-cut evidence is available regarding mortality or morbidity benefit in patients with NSTI.

NSTI is an uncommon disease with a high morbidity and mortality rate. It requires a high index of suspicion for diagnosis and prompt, simultaneous initiation of surgical intervention, broad-spectrum antimicrobials, fluid resuscitation, and supportive care.

MENINGITIS AND ENCEPHALITIS

Acute community-onset meningitis is clinically defined as a syndrome characterized by the onset of meningeal symptoms over hours to a few days. The classic triad includes fever, nuchal rigidity, and altered mental status, although individual symptoms are commonly present but can vary based on age and

underlying conditions. The most common causes of acute meningitis are viruses (ie, enteroviruses, mumps, and herpes simplex virus). The most common bacterial causes, *H influenzae*, *Neisseria meningitides*, and *S pneumoniae*, account for more than 80% of cases. Although vaccinations have considerably reduced the incidence of bacterial meningitis, case-fatality rates have not changed significantly.

H influenzae meningitis has dramatically decreased in incidence following the introduction of vaccination, and *H influenzae* currently is isolated in 7% of bacterial meningitis cases. *N meningitidis* typically causes infections in children and young adults. Recent outbreaks among college-age students with serogroup B illustrate the sporadic nature of infection. Commercially available vaccines previously covered serogroups A, C, W, and Y, although the most common endemic serogroups in the United States are B, C, and Y. Two recently introduced vaccines offer coverage against serogroup B. Although the typical mortality rates for meningococcal infections range from 3% to 13%, a fulminant form of meningococcemia can result in mortality rates as high as 70%, with most deaths occurring at unrelenting rapidity within 48 hours. *S pneumoniae* is the most frequently encountered agent of bacterial meningitis, accounting for nearly 60% of cases and resulting in a 20% to 30% mortality rate.

Acute encephalitis shares many of the same clinical features as acute meningitis. Because the cerebral cortex is diffusely involved in patients with encephalitis, changes in mental status occur much more commonly in patients with encephalitis. Confusion, behavioral and speech disturbances, focal neurological deficits, and seizures are common in encephalitic patients, although the syndrome may coexist in the form of meningoencephalitis. Viruses, typically herpesviruses (herpes simplex virus, varicella zoster virus, cytomegalovirus, human herpesvirus 6), arboviruses (West Nile, eastern equine, St Louis, La Crosse, and Japanese encephalitis), HIV, rabies, and enteroviruses, are the predominant causes for acute encephalitis.

The diagnostic workup should include a complete history and physical examination. A lumbar puncture is essential. Neuroimaging is warranted before lumbar puncture if there is suspicion that the clinical presentation may be secondary to an intracranial mass lesion with mass effect. This includes new-onset seizures or focal neurological deficits, history of central nervous system lesions, immunocompromised state, papilledema, or progressive neurological deterioration. If mass effect is suspected, treatment should not be delayed for diagnostic purposes.

Patients may or may not have peripheral leukocytosis. A cerebrospinal fluid (CSF) opening pressure should be determined. CSF should be analyzed for cell count, protein, and glucose levels. Gram stain and bacterial cultures should be obtained for all patients. When results of the CSF cell count are analyzed, it is important to note whether the sample was obtained during a traumatic or an atraumatic tap. If the sample was the product of a traumatic tap, the WBC count could be falsely elevated. Peripheral blood in the CSF after a traumatic tap will result in an artificial increase in WBC count by 1 WBC for every 500 to 1,000 red blood cells (RBCs) in the CSF. A ratio of observed CSF WBCs to predicted WBCs (Predicted = CSF RBCs × [Blood WBCs/Blood RBCs]) can be used to correct for traumatic lumbar puncture.

Gram stain examination of CSF can rapidly and accurately identify the causative organism in 60% to 90% of patients with bacterial meningitis with a specificity of nearly 100%. CSF culture is the gold standard in diagnosis and is positive in nearly 90% of patients with community-acquired bacterial meningitis if obtained prior to antimicrobial therapy. PCR assays are increasingly more promising alternatives to viral cultures in the diagnosis of enteroviral meningitis and herpes encephalitis. In addition, broad-based bacterial PCR can be used to detect the most common microorganisms of bacterial meningitis in a single test with adequate sensitivity and high specificity.

If purulent meningitis is suspected, initiation of empirical antimicrobial therapy should be based on the patient's age and underlying disease status or following the results of Gram staining. Penicillin alone is never recommended as initial empirical therapy. Generally, a third-generation cephalosporin alone is used for *H influenzae* type b, *N meningitides*, and *E coli.* The addition of vancomycin to a third-generation cephalosporin is recommended for *S pneumoniae* primarily due to the emergence of resistant pneumococcal strains. Ampicillin or penicillin G with or without an aminoglycoside is recommended for treatment of *Listeria monocytogenes* and *Streptococcus agalactiae.* Empirical treatment of gram-negative meningitis should begin with ceftazidime, cefepime, or meropenem. Certain patients with bacterial meningitis, particularly pneumococcal meningitis, should be treated with adjunctive dexamethasone.

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CHAPTER 29

Liver Failure, Gastrointestinal Bleeding, and Acute Pancreatitis

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Key words: liver failure, liver transplant, gastrointestinal bleeding, peptic ulcer, esophageal varices, pancreatitis

LIVER FAILURE

Acute liver failure (ALF) affects approximately 2,000 to 3,000 patients yearly in the United States.[1] ALF is defined as the onset of hepatic encephalopathy and coagulopathy within 26 weeks of jaundice in a patient without preexisting liver disease.[2] ALF is to be distinguished from primary hepatic failure in patients with a history of preexisting liver disease and cirrhosis. These patients often present with one or more complications of chronic liver disease (gastrointestinal [GI] bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, or renal failure) as a result of an acute exacerbation of their underlying liver disease (decompensated Wilson's disease, reactivation hepatitis B, or autoimmune hepatitis). ALF can occur as a consequence of primary organ failure or secondary to multiple organ dysfunction syndrome.

Causes

ALF can be classified into 3 etiological categories: infectious, substance induced, and miscellaneous. Infectious causes of ALF include hepatitis viruses A through G, coxsackieviruses, echoviruses, adenoviruses, and parvovirus B19. Substance-induced hepatic failure most commonly occurs secondary to drug toxicity, with acetaminophen being the most common cause. Other toxins causing ALF include alcohol, aflatoxin, carbon tetrachloride, and toxins that present in certain wild mushrooms. Disease processes such as Budd-Chiari

syndrome (thrombotic occlusion of hepatic veins), Wilson disease, fatty liver of pregnancy, Reye syndrome, and autoimmune hepatitis can cause ALF.

Management

Patients should be admitted to the hospital when ALF is accompanied by significant hepatic derangement (international normalized ratio [INR] >1.5). The onset of hepatic encephalopathy should warrant admission to an ICU because neurological deterioration can be rapid. Tests should be performed to exclude other diseases that can mimic ALF.

Treatment is generalized and supportive until complications develop. Patients with impending hypoxemia or hypercapnia should be placed on mechanical ventilation. Volume status should be optimized. Neurological evaluation should be performed frequently. Laboratory values such as electrolytes, complete blood count, liver panels, and coagulation panels should be drawn up to every 6 hours. Nutrition should be maintained if no contraindications exist, and the enteral route is preferred. Urine output and laboratory results for renal evaluation should be monitored closely and dialysis instituted if indicated. Patients with an unstable hemodynamic status should be placed on continuous renal replacement therapy.

Antidotes may be used for ALF in certain instances where the disease is caused by a particular toxin. The antidote with the strongest data supporting its use in ALF remains *N*-acetylcysteine (NAC) in patients with acetaminophen overdose. NAC should be administered even if the timing, dose, or plasma concentration of acetaminophen is unclear. Intravenous NAC should be administered in patients with greater than grade 1 encephalopathy or hypotension or if oral dosing is not tolerated. Therapy should continue until resolution of hepatic encephalopathy, INR less than 1.5, and declining transaminases. Clinical improvement dictates length of treatment, which can exceed 96 hours.[2] Recently, a multicenter, double-blind randomized trial of NAC in non–acetaminophen-induced ALF demonstrated improved nontransplant survival in patients treated early in the course of their disease with low-grade encephalopathy.[3] The trial entailed patients with ALF and encephalopathy.

Numerous other disease-specific treatments have been used, including corticosteroids for autoimmune hepatitis, lamivudine for hepatitis B–related ALF, and acyclovir for herpes simplex ALF.[4] However, randomized data supporting the use of these therapies are sparse. In pregnant patients, prompt

delivery of the fetus reverses ALF in women with acute fatty liver of pregnancy or the HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count).[5]

Prognostic Evaluation

A critical management decision remains whether a patient with ALF should be listed for a liver transplant. Several prognostic criteria have been developed to predict outcome after medical management. The King's College criteria remain the most widely applied parameters to predict prognosis of patients with ALF (**Table 1**).[6] Liver transplant should be promptly considered in patients with a poor prognosis.

Table 1. King's College Hospital Prognostic Criteria Predicting Poor Outcome in Acute Liver Failure

Acetaminophen-Induced ALF pH <7.3 after fluid resuscitation *or* all of the following features:
PT >100 seconds (INR >6.5)
Serum creatinine >3.4 mg/dL
Grade 3 or 4 hepatic encephalopathy
Non–Acetaminophen-Induced ALF Any 3 of the following:
Age <10 or >40 years
Origin: non-A hepatitis, non-B hepatitis, halothane hepatitis, drug toxicity
PT >50 seconds (INR >3.5)
Serum bilirubin >17.5 g/dL

Abbreviations: ALF, acute liver failure; INR, international normalized ratio; PT, prothrombin time.

Management of Complications

Cerebral Edema and Intracranial Hypertension

Intracranial hypertension (ICH) accounts for 20% to 25% of deaths in ALF and can lead to residual neurological deficits after recovery.[7] The pathophysiological process of cerebral edema is incompletely understood and is thought to involve osmotic and hemodynamic alterations secondary to astrocyte conversion of ammonia to glutamine. ICH has the highest incidence in patients in an acute

presentation (progression from jaundice to encephalopathy in <4 weeks). Computed tomography (CT) scan of the head is recommended for patients with grade 3 or 4 encephalopathy, patients with acute mental status changes, or prior to intracranial pressure (ICP) monitoring. This study is primarily performed to rule out bleeding.[2]

Insertion of ICP monitors in patients with ALF remains a controversial topic. Advocates of ICP monitor placement recommend its use as a consideration for potential transplant. According to these clinicians, high ICP (>25 mm Hg) and a low cerebral perfusion pressure (<40 mm Hg) that continues for more than 2 hours carries a poor prognosis that can contraindicate transplant.[8] Opponents note that ICP monitor placement is associated with a risk of bleeding and has not improved outcome in nonrandomized trials.[9,10] This risk may be low; some studies cite the risk of clinically significant intracranial bleeding in this setting as less than 5%.[11,12]

One of the first steps in medical prevention of cerebral edema includes active aggressive management of the hepatic encephalopathy. Intubation, bowel cleansing with lactulose,[2] and head of the bed elevation greater than 30° have been advocated. Orally administered lactulose or rifaximin may lower serum ammonia levels; however, the efficacy of these agents remains unproven and they may have concurrent adverse effects.[2] Patients with body temperature greater than 39°C (102.2°F) should be treated with cooling blankets. Hypothermia should not be reversed unless the temperature is below 34°C (93.2°F). Severe hyponatremia—less than 130 mg/dL—should be corrected with hypertonic saline to normalize serum sodium levels to the 140 to 150 mEq/L range. Seizures can exacerbate increased ICP; however, studies examining the utility of prophylactic phenytoin in ALF provided uncertain benefit.[13,14] Consequently, antiepileptic agents are not routinely recommended in this population.

Upon the onset of ICH (ICP >25 mm Hg), IV mannitol or hypertonic saline should be administered to draw intracerebral fluid into the intravascular space. Prolonged osmotic therapy may be required as a bridge to liver transplant. If osmotic measures fail, deep sedation induction with propofol or barbiturates, IV indomethacin, and therapeutic hypothermia has been described. Total hepatectomy has been advocated in patients who are refractory to all medical measures and have already been allocated a liver graft.[15]

Infection

Prevention and treatment of infections are mandatory in the therapy of ALF. Infectious complications are common in patients with ALF secondary to immune dysfunction. Fifty percent of infections are pneumonia, 22% urosepsis, 12% catheter-related bacteremia, and 16% spontaneous bacteremia.[16] Routine signs of infection, however, may be absent in up to one-third of individuals. Although studies have been inconclusive regarding the benefit of prophylactic antibiotics, current practice guidelines support minimizing invasive lines; conducting frequent surveillance cultures of blood, urine, and sputum; and using empirical broad-spectrum antibiotics in grade 3 or grade 4 encephalopathy, renal failure, or any component of the systemic inflammatory response syndrome. Prophylactic antibiotics are also administered to patients awaiting liver transplant because infection can preclude transplant.[17]

Pulmonary Considerations

Airway management is of paramount consideration in ALF patients. Nonintubated patients with ALF should be placed on aspiration precautions, and the head of the bed should be elevated. Patients with grade 3 encephalopathy should have airway protection by endotracheal intubation. Acute lung injury and acute respiratory distress syndrome (ARDS) occur in approximately one-third of patients and can cause profound hypoxemia and hypercapnia. However, despite the vasodilatory effects of an elevated $Pa\text{CO}_2$, permissive hypercapnia to offset worsening lung injury outweighs the consequences of elevated ICP. Hypoxemia leading to ARDS should be treated by individual institutional protocols for ARDS management that include intubation and recruitment maneuvers such as increasing mean airway pressure by elevating positive end-expiratory pressure. In patients with ARDS, clinicians should optimize the patient's cardiovascular status by ensuring proper preload status and using a pulmonary artery catheter if necessary. In some centers, fluid removal with continuous veno-venous hemodialysis or enhanced oxygenation by extracorporeal oxygenation membrane can be useful.[18]

Bleeding

Coagulopathy in patients with ALF is common, involving abnormalities of the clotting cascade as well as both quantitative and qualitative platelet dysfunction; however, clinically significant bleeding is less common.[2] Empirical vitamin K is recommended in all patients. Correction of coagulopathy to an INR less than 1.5 and platelet count greater than 50,000/mm^3 in patients with clinically significant bleeding or before placement of invasive devices is recommended. Prophylactic

fresh frozen plasma is not indicated and can mask liver deterioration and the need for transplant. Cryoprecipitate is recommended in patients with significant hypofibrinogenemia (<150 mg/dL, or <200 mg/dL with clinical bleeding present). In patients for whom fresh frozen plasma is unable to correct the coagulopathy, commercially available multifactor products such as Kcentra (CSL Behring, USA) should be administered prior to a procedure. Recombinant factor VIIa has been shown to increase risk of thrombotic complications in patients with ALF.[19,20] Upper GI bleeding (UGIB) in ALF patients has been shown to be decreased with acid reduction therapy, so either histamine 2 receptor antagonists or proton pump inhibitors should be administered prophylactically for these critically ill patients.[21]

Additional considerations include optimizing cardiovascular and nutritional status in these patients. Hypotension is addressed with assessment of volume status and is corrected prior to initiation of vasopressor support. Norepinephrine and neosynephrine are preferred; norepinephrine is the vasopressor of choice in patients with traumatic brain injury.[22] Enteral nutrition is recommended with regimens of high caloric density to minimize volume administration.

Transplantation

Liver transplantation has dramatically improved mortality rates in patients with ALF, increasing the survival rate to greater than 80% at 1 year.[4]

Selection criteria to identify patients likely to benefit from emergency liver transplant remain controversial. Inappropriate allocation of a liver to a patient not requiring a transplant has the consequences of subjecting the patient to lifelong immunosuppression. Additionally, the organ may have been used in a more appropriate patient with a higher mortality expectancy without transplant. Several different criteria are used to identify liver transplant candidates. The King's College Hospital prognostic criteria (**Table 1**) remain among the most commonly applied.[4] These criteria have been confirmed to have clinically acceptable specificity, and patients meeting these criteria who do not undergo transplant have survival rates of less than 15%.[23-25] Despite this, certain patients may not be identified through these criteria. Hence, additional markers and scoring systems, including the model for end-stage liver disease score, have been suggested as alternate criteria for patient stratification and are commonly used in the United States.[26-29]

Outcomes after liver transplant in ALF are governed by 3 primary factors:

recipient age, illness severity, and the nature of the donor graft. Postoperative mortality more than doubles in recipients older than 50 years.[23,30] Poorer pretransplant illness severity correlates with posttransplant success. Graft factors also weigh in heavily on posttransplant outcomes, with inferior outcomes noted in smaller, ABO-incompatible, and steatotic grafts.[4]

Auxiliary liver transplant has been proposed as an alternate treatment for ALF. This technique involves either heterotopic or orthotopic placement of a partial liver graft, with all or part of native liver left in situ. The rationale with this technique is to allow the native liver to regenerate after resolution of the initial liver insult. This is a technically demanding procedure, with high complication and retransplant rates.[31] Most liver transplant centers consider auxiliary transplant in younger patients who have specific cause-related liver failure with stable extrahepatic organ dysfunction.[4]

Living-donor transplantation is used to treat ALF, primarily in the pediatric population. This technique has the primary advantage of increased speed of organ availability, allowing for rapid transplant. In adults, living-donor emergency transplantation has been reported to have up to 80% 5-year survival rates.[32,33] Numerous ethical and psychosocial considerations exist regarding adult living-donor transplantation, with most successful procedures involving transplant of right-lobe grafts, although right-lobe grafts may have more complications than left-lobe or left-lateral segment grafts, which are commonly used in the pediatric population.

Extracorporeal liver support devices have been used in patients. However, these techniques remain investigational as no clear survival benefit has been demonstrated.[34-36] Human hepatocyte transplantation has been suggested to treat ALF and is an area of active research.[37]

GASTROINTESTINAL BLEEDING

GI bleeding is a common disease entity that requires surgical consultation. GI bleeding can be divided into 2 categories—upper and lower GI bleeding. UGIB is defined as bleeding occurring proximal to the ligament of Treitz.

Initial Management

Patients with GI bleeding demonstrate a broad spectrum of initial clinical presentations, ranging from normal vital signs to extremis. Initial management is

dictated by the perceived rate of bleeding and the degree of hemodynamic stability. Hemodynamically stable patients with no evidence of active bleeding can be considered for evaluation on an outpatient basis. Patients who demonstrate signs of active bleeding and hemodynamic instability require intensive monitoring, aggressive supportive care, and a proactive approach to determine the source of the bleeding.

Standard initial evaluation of a patient with GI bleeding should include assessment of the airway, breathing, and circulation. Patients with severe blood loss may demonstrate significant tachypnea. Early intubation should be performed for any signs of respiratory distress or hypoxia. Large-bore IV access should be obtained for resuscitation. Central venous catheterization including large-caliber cordis catheters may be necessary in unstable patients for resuscitation and hemodynamic monitoring. Urinary catheters should be placed to assist in monitoring resuscitation. Management includes resuscitation with isotonic fluids and packed red blood cells (RBCs) as needed and correction of coagulation factors.

Localization of the bleed becomes urgent in critically ill patients with GI bleeding. Nasogastric lavage allows for localization of UGIB given that bloody aspirate is generally an indication of bleeding proximal to the ligament of Treitz. To exclude an UGIB source, the nasogastric aspirate must be nonbloody and bilious because nonbilious aspirate can indicate bleeding distal to the pylorus. However, the sensitivity and specificity for using nasogastric aspirate to determine the upper or lower nature of the bleeding can be highly variable. Definite localization of UGIB warrants an upper endoscopy. If localization does not reveal an UGIB source, further investigation should be performed with a lower endoscopy.

Upper Gastrointestinal Bleeding

More than 400,000 patients are hospitalized yearly for acute UGIB.[38] The majority of cases of UGIB are secondary to peptic ulcer disease.[39] Esophageal and gastric varices, Mallory-Weiss tears, hemorrhagic gastritis, neoplasms, Dieulafoy lesions, hemobilia, duodenal diverticula, and aortoenteric fistulas are other causes of UGIB.

Evaluation and Risk Stratification

Upper endoscopy is effective at localizing and controlling UGIB. Endoscopic

evaluation can also be performed for initial workup, given that the false-negative rate for nasogastric aspirates has been reported at 15%.[40] To allow for risk stratification of patients on initial presentation, numerous scoring systems have been developed, including the Blatchford score and the Rockall score.[41,42] The Forrest classification has been used to predict the likelihood of rebleeding based on the appearance on initial endoscopy.[39] Greater than a third of patients present with high-risk lesions, which have reported rebleeding rates of 22% to 55% if left untreated.[43-45]

Therapeutic maneuvers to control bleeding include injection treatments (vasoconstrictors, sclerosing agents, tissue adhesives, saline), thermal coagulation, sclerotherapy, and mechanical occlusion, such as application of variceal bands or hemostatic clips. If endoscopic therapy fails to control bleeding on first attempt, a second attempt should be made, because this is associated with fewer complications than proceeding with a surgical option.[46] Acute surgical intervention is often warranted in bleeding patients with hemodynamic instability or severe bleeding (>6-U transfusion requirement within 48 hours) with failure to control the bleeding endoscopically. Recently, interventional radiologic techniques have been used as an adjunct to the maneuvers to control bleeding.[47]

Peptic Ulcers

Peptic ulcers are the most frequent cause of acute UGIB.[39] Peptic ulcers are anatomically classified as duodenal ulcers and gastric ulcers. Duodenal ulcers most commonly cause bleeding due to ulcer erosion into the posterior duodenal wall and the gastroduodenal artery. Surgical hemostatic control can be achieved through an anterior longitudinal duodenotomy. The method of suture varies, but the surgical principle is to constrict the multifaceted source of bleeding. Often, the primary culprit is a side branch of the gastroduodenal artery, but cross-feeding and back-bleeding collaterals can also perpetuate the bleeding. One technique uses placement of nonabsorbable sutures proximal and distal to the site of bleeding with a third suture then placed posteriorly to control a posterior branch, which is often the transverse pancreatic artery. Another technique uses 2 “U-stitches” placed over the site of bleeding at 90° each to control all the conduits to the bleeding area.

With the advent of potent acid-suppressing proton pump inhibitors (PPIs), acid reduction surgery to prevent rebleeding has become less prevalent.[48,49] Acid suppression has been shown to promote clot formation and prevent platelet

disaggregation and fibrinolysis.

Recent meta-analyses have shown that the acid reduction achieved with PPI therapy significantly decreases the risk of rebleeding, the need for surgery, and death.[50,51] Hence, although PPIs and surgical acid reduction have not been compared in a prospective fashion, PPIs have replaced acid reduction surgery in the acute setting in patients not receiving preoperative acid reduction pharmacotherapy. In patients receiving PPIs who develop severe peptic ulcer bleeding, acid reduction surgery is indicated. The surgical options here include truncal, selective, or highly selective vagotomy and drainage (pyloroplasty, antrectomy with Billroth I or II, or Roux-en-Y). For many patients with bleeding duodenal ulcers that require surgery, the operation of choice is a vagotomy with pyloroplasty and oversewing of the ulcer through the gastroduodenotomy incision.

The surgical management of gastric ulcers varies based on their cause and location. Type I gastric ulcers are located on the lesser curvature, are not associated with acid hypersecretion, and are often treated with a wedge resection as the procedure does not generally cause a luminal compromise. Type II gastric ulcers can have 2 locations—along the lesser curve of the stomach and in the duodenum. Type III are prepyloric ulcers and are associated with acid hypersecretion. Type II and III ulcers are best treated with truncal vagotomy and antrectomy. Type IV ulcers are located on the lesser curve near the cardia and esophagogastric junction. Distal gastrectomy with a tongue-shaped extension along the lesser curve and a Roux-en-Y reconstruction (Csendes procedure) may be necessary. Type V ulcers are diffuse ulcers related to the use of nonsteroidal anti-inflammatory drugs. In addition to ulcer excision, medical or surgical acid suppression should be instituted when a patient demonstrates hypersecretion of acid.

Angiography with embolization of the bleeding vessel is an option to control bleeding. Various embolization particles such as coils, gel foam, and polyvinyl alcohol are used. Technical success rates ranging from 52% to 94% with a 10% rebleeding rate have been reported.[47] Angiographic control has been shown to be equivalent to surgery after endoscopic failure.[52]

Esophageal Varices

Gastroesophageal varices are prevalent in almost 50% of patients with cirrhosis. The 1-year rate of a first variceal hemorrhage is approximately 12%.[53] The rate

of recurrent variceal hemorrhage at 1 year is approximately 60%, and the 6-week mortality after each episode of hemorrhage ranges from 15% to 20%.[54-56]

Patients presenting with acute variceal hemorrhage should receive pharmacotherapy aimed at reducing splanchnic pressure, namely vasoconstrictive agents such as vasopressin or octreotide. Nitroglycerin is often used as an adjunct to reduce cardiac side effects of vasopressin. Endoscopic therapy through either band ligation or sclerotherapy is the next step to control bleeding and is successful in up to 80% of cases. If 1 or more endoscopic attempts are unable to control severe acute variceal bleeding, placement of a balloon tamponade agent (Minnesota tube or Sengstaken-Blakemore tube) is indicated. These tamponade agents should not be maintained for more than 48 hours because they can lead to esophageal or gastric perforation or necrosis.

The inability to control an acute variceal hemorrhage or a recurrent variceal bleed after endoscopy is an indication for transjugular intrahepatic portosystemic shunt (TIPS). This involves creating a portosystemic shunt by placing a stent connecting a hepatic vein to a branch of the portal vein. The efficacy of TIPS as salvage therapy in the setting of pharmacotherapeutic and endoscopic failure is well established.[57] Two recent randomized controlled trials have shown that early TIPS in high-risk patients (Child class C and Child class B with persistent bleeding at endoscopy) is associated with improved survival. Hence, early shunt placement should be considered in this patient population.[58,59]

After TIPS, surgical therapy should be considered in patients with severe portal hypertension or recurrent variceal bleeding. Surgical options include portosystemic shunts, orthotopic liver transplantation, and esophagogastric devascularization. Patients who are transplantation candidates (most Child A and B patients) are best treated with orthotopic liver transplant.

Historically, many different shunts were used to decrease the portal pressure, but these procedures are rarely performed nowadays. Nonselective portosystemic shunts such as end-to-side or side-to-side portocaval shunts, interposition mesocaval shunts, and conventional splenorenal shunts are effective at controlling refractory hemorrhage but are associated with higher rates of hepatic encephalopathy and hepatic failure. The selective distal splenorenal shunt (DSRS) has been reported in several clinical trials to demonstrate significantly lower rates of encephalopathy compared with nonselective shunting; however, DSRS is believed to contribute to ascites formation due to the extensive retroperitoneal dissection and is contraindicated in patients with refractory

ascites or splenic vein thrombosis. In patients who are future transplant candidates and have TIPS-refractory bleeding, mesocaval or DSRS shunts are used to control bleeding. In patients who are not future transplant candidates and have minimal ascites, a DSRS is constructed. Nonselective shunts are also used in patients with intractable ascites, as in Budd-Chiari syndrome.

Esophagogastric devascularization is an effective nonshunt operation to prevent recurrent variceal hemorrhage and is used in patients with splanchnic vein thrombosis that precludes a shunt procedure. The Sugiura procedure involves ligation of venous branches entering the distal esophagus and proximal stomach, selective vagotomy, and pyloroplasty, preserving the left gastric and paraesophageal collateral veins to allow for porto-azygous collateralization. Operative mortality in the United States for this procedure has exceeded 20%, and 35% to 55% of procedures entail recurrent bleeding; thus, this procedure is used only in patients who are unable to undergo shunting because of extensive splanchnic vein thrombosis.[60,61]

Lower Gastrointestinal Bleeding

If nasogastric lavage and endoscopy do not yield an upper GI source, diagnostic testing to determine the lower GI source of bleeding should be initiated.

Colonoscopy

In the United States, the incidence of lower GI bleeding (LGIB) ranges from 20.5 to 27 cases per 100,000 adults.[62] Compared with patients who have UGIB, patients with LGIB are less likely to experience shock, will require fewer transfusions of packed RBCs, and are more likely to experience spontaneous resolution of bleeding. Mortality from LGIB ranges from 2% to 4%.[63] The most common origins of LGIB are colonic diverticula, angiodysplasia, various forms of colitis, neoplasia, anorectal disease, and small bowel bleeding.[64]

Diagnosis

Colonoscopy is recommended as the first modality to diagnose LGIB. The diagnostic yield of colonoscopy has been reported at 89% to 97%.[65,66] Colonic cleansing prior to colonoscopy is recommended because this facilitates endoscopic visualization and therapeutic interventions.[67] Full colonoscopic evaluation is recommended given that bleeding sources in the right colon are common. The ileocecal valve should be intubated because blood in the terminal

ileum suggests a small bowel source. If traditional upper and lower endoscopy does not localize a source, push enteroscopy can be used, which allows for visualization of 50 to 120 cm of proximal jejunum. Diagnostic yield of push enteroscopy has been reported from 13% to 78%.[68] Double-balloon enteroscopy and video capsule endoscopy allow for full visualization of the small intestine.

Different types of angiographic procedures can be used to localize active GI bleeding. In the case of more rapid bleeding (0.5-1 mL/min), mesenteric angiography can provide for localization of the bleeding source. Angiography is 100% specific but less sensitive, varying from as low as 47% in acute LGIB to 30% in recurrent bleeding. Bleeding vessels can be marked for intraoperative identification by injecting the bleeding vessel with methylene blue. Recently, CT angiography has been used to detect acute LGIB and appears to have accuracy rates comparable to those of visceral angiography—54% to 79%.[69-71] Since CT angiography is much less invasive than mesenteric angiography, it is sometimes performed initially to localize bleeding.

Nuclear scintigraphy can be used if the rate of bleeding is slower but still active (<0.5 mL/min). Nuclear tagged RBC scans are more sensitive but less specific than angiography[64] and have an advantage over angiography in that they are noninvasive. Variable accuracy rates have been reported, ranging from 48% to 97%.[72,73] Nuclear tagged RBC scans have the disadvantages of not allowing simultaneous therapeutic interventions and of localizing bleeding only to an area of the abdomen; however, these scans can be instrumental in localizing bleeding and allowing a selective surgical resection. In many institutions, RBC scans are more readily available than angiography and thus may be considered an earlier option. Nonetheless, in many patients who can receive a bowel preparation, colonoscopy remains the first-line therapy of choice in LGIB and can be both diagnostic and therapeutic.

Therapy

Several modalities for endoscopic therapy for LGIB are available, including thermal coagulation using monopolar or bipolar electrocoagulation, argon plasma coagulation, injection of epinephrine to promote local vasoconstriction, and placement of metallic clips.

Angiographic therapy includes both transcatheter embolization techniques and intra-arterial vasopressin injection. Angiography is used to control lower GI hemorrhage in patients with massive bleeding with hemodynamic instability

precluding colonoscopy or an inability to localize the bleeding lesion colonoscopically. The introduction of microcatheters has allowed for selective embolization without the risk of bowel infarction.[74] Newer embolization techniques are available, including microcoils, gel foam, and polyvinyl alcohol particles. Success rates range from 70% to 90%,[74] with recurrence rates less than 15%.[62] Patients who receive any visceral embolization need to be monitored for segmental intestinal ischemia for at least several days.

Surgical therapy for LGIB is not commonly performed. Hemodynamic instability with inability to control bleeding, severe bleeding (>6-U transfusion requirement), and failure of nonoperative therapies to control bleeding are all indications for surgery. Blind or total colectomies without definitive localization should be avoided given that segmental colectomies are associated with decreased morbidity, mortality, and rates of rebleeding.[75] Intraoperative endoscopy should be performed, which allows for localization of bleeding in patients in whom preoperative localization was unsuccessful. If the site of bleeding cannot be determined despite these measures, the procedure of choice is a subtotal colectomy. However, this is associated with mortality rates ranging from 5% to 33%.[76]

ACUTE PANCREATITIS

Acute pancreatitis is an acute inflammatory process of the pancreas. The annual incidence in the United States has been estimated to be approximately 200,000 cases per year.[77] Although overall mortality remains less than 1%, as many as 20% of patients develop severe acute pancreatitis, which is associated with a mortality rate from 10% to 25%.[78] Pancreatitis can be accompanied by local complications, including pancreatic necrosis with infection, and by systemic sequelae including marked changes in fluid homeostasis, systemic inflammatory response syndrome, respiratory compromise, and multiple-organ dysfunction syndrome.

Pathophysiological Processes and Causative Agents

Current understanding of the pathophysiological processes of acute pancreatitis suggests that a common cascade of cellular derangements follows varied causes of initial injury. Pancreatic injury leads to intra-acinar cell cleavage of proteolytic enzymes, most notably trypsinogen to trypsin, causing acinar cell injury. Cellular injury leads to local release of trypsin, catalyzing further activation of proteolytic enzymes within pancreatic parenchyma, compounding

cell damage. Neutrophils and macrophages infiltrate pancreatic parenchyma and lead to a local inflammatory response with release of interleukin 1β, interleukin 6, interleukin 8, tumor necrosis factor α, platelet activating factor, complement, bradykinin, nitric oxide, reactive oxygen intermediates, and substance P.[79] These inflammatory mediators maintain a robust inflammatory response, which contributes to further parenchymal damage. As a consequence of these events, pancreatic autodigestion and pancreatic necrosis develop.

In the United States, up to 40% of cases of acute pancreatitis are attributed to alcohol and 35% to gallstones. The risk of developing pancreatitis increases as the dose of alcohol increases. Despite this, only a minority of alcoholics develop pancreatitis, pointing to additional factors that may synergize with alcohol to induce cellular injury. The pancreas metabolizes alcohol through both oxidative and nonoxidative mechanisms. Excessive alcohol and its metabolites may lead to intra-acinar cell proteolytic enzyme activation, initiating injury. Identification of factors to stratify patients at high risk for developing alcoholic pancreatitis is an area of active research. In biliary pancreatitis, the inciting factor is thought to be obstruction of the ampulla of Vater leading to increased pressure within the pancreatic duct. Even in the absence of gallstones, biliary sludge or microlithiasis (<5-mm-diameter stones) can contribute to acute pancreatitis. Numerous other causes of acute pancreatitis have been identified (**Table 2**).

Table 2. Causes of Acute Pancreatitis

Gallstones
Alcohol
Neoplasms
Trauma
Pancreas divisum
Medications
Toxins (scorpion venom)
Infectious agents
Genetic factors (hereditary pancreatitis, cystic fibrosis)
Vasculitis (systemic lupus erythematosus, polyarteritis nodosa)
Iatrogenic factors (endoscopic retrograde cholangiopancreatography, cardiopulmonary bypass)

Presentation

Patients typically present with the acute onset of epigastric pain, often radiating to the back, with associated nausea and vomiting. The presence of fever can suggest development of an intrapancreatic infection. Jaundice can suggest a biliary origin of pancreatitis, underlying liver disease, or possibly a biliary stricture related to chronic pancreatitis. Epigastric tenderness and abdominal distention secondary to a colonic ileus are common. The presence of ecchymosis along the flank (Grey-Turner sign), inguinal ligament (Fox sign), or umbilicus (Cullen sign) can suggest the development of hemorrhagic pancreatitis, but these signs are rarely seen at initial presentation.

Diagnosis

Early diagnosis of patients with acute pancreatitis is essential to allow for appropriate risk stratification and initiation of appropriate supportive care. Biochemical tests remain the mainstay in the initial diagnosis. Imaging studies are used to identify biliary pancreatitis or possible complications of acute pancreatitis.

Biochemical Tests

Local acinar cell injury is accompanied by systemic release of pancreatic digestive enzymes. Among these, pancreatic amylase is commonly used in the diagnosis of acute pancreatitis. With onset of acute pancreatitis, serum amylase levels increase rapidly and can normalize within days given the relatively short half-life of serum amylase (10 hours). Elevation of amylase is not specific for pancreatitis and can be seen with other GI abnormalities such as perforated ulcer, small bowel obstruction, acute renal failure, and salivary glandular disease. Elevation in amylase to more than 3 times the upper limit of normal is almost always a result of acute pancreatitis.

Pancreatic lipase is another pancreatic digestive enzyme used in the diagnosis of acute pancreatitis. Lipase levels parallel amylase; however, lipase has a longer half-life than amylase and can be useful in diagnosing a delayed presentation of acute pancreatitis.

More specific biochemical tests are less widely used but have been described. Serum interleukin 6 levels greater than 400 pg/mL on admission have a negative predictive value (NPV) of 93%. Polymorphonuclear leukocyte elastase levels greater than 300 μg/L at 24 hours have an NPV of 98%, whereas the NPV is 89% for urinary trypsinogen activation peptide at 24 hours and 90% for serum

C-reactive protein greater than 150 mg/dL at 24 hours.[80]

Radiological Tests

Plain radiographs are nonspecific for pancreatitis, although abdominal films may demonstrate loops of dilated small intestine ("sentinel loop") or large intestine ("colon cutoff sign"). Chest radiographs may demonstrate pleural effusions in the setting of pancreatitis.

Ultrasonography may demonstrate an enlarged pancreas; however, overlying bowel can obscure visualization. Ultrasound is the diagnostic test of choice to evaluate for the presence of gallstones as a possible cause of pancreatitis and biliary ductal dilatation. CT is a useful adjunct in severe acute pancreatitis and is indicated to assess disease severity, detect complications, and provide image guidance for radiological procedures. CT is also useful in differentiating pancreatitis from other conditions presenting with abdominal pain and elevated pancreatic enzymes. Contrast-enhanced CT imaging with a pancreatic phase injection is more than 90% sensitive in assessing for areas of necrotic pancreas and is indicated in severe pancreatitis or in the absence of clinical improvement.

Magnetic resonance imaging and magnetic resonance cholangiopancreatography are being used increasingly to evaluate patients with acute pancreatitis. These modalities can be beneficial in patients with a contraindication to ionizing radiation or iodinated contrast. Additionally, these techniques provide superior anatomic delineation of the pancreas and biliary tree compared with CT scanning. Magnetic resonance cholangiopancreatography is specifically used to exclude the presence of choledocholithiasis. However, given its lower cost, shorter duration, and easier availability, CT scan remains the imaging test of choice to evaluate for most complications of pancreatitis.

Assessment of Severity

Serum biochemical markers are used to stratify disease severity in acute pancreatitis. The Atlanta classification has been used to categorize acute pancreatitis as mild or severe.[81] Severe pancreatitis is defined as any 1 of the following[82]: (1) organ failure with 1 or more of the following: shock (systolic blood pressure <90 mm Hg), hypoxemia (Pa_{O_2} <60 mm Hg), renal failure (serum creatinine >2 mg/dL), and GI bleeding (>500 mL in 24 hours); (2) local complications such as pancreatic necrosis, pseudocyst, or abscess formation; (3) at least 3 Ranson criteria (**Table 3**); or (4) at least 8 of the Acute Physiology and

Chronic Health Evaluation (APACHE II) criteria.[83]

Table 3. Ranson Criteria

On admission
Age >55 years
White blood cell count >16,000/mL
Glucose >200 mg/dL
Serum lactate dehydrogenase >350 IU/L
Aspartate aminotransferase >250 IU/L
During initial 48 hours
Serum calcium <8 mg/dL
Hematocrit decrease >10%
PaO_2 <60 mm Hg
Base deficit >4 mEq/L
Blood urea nitrogen increase >5 mg/dL
Fluid sequestration >6 L

The Ranson criteria are widely used to stratify disease, and they correlate well with morbidity and mortality rates.[84] A Ranson score of 3 or greater is associated with severe disease. The modified Glasgow scale has also been developed, with a score of 3 or more correlating with severe disease.[85] The APACHE II scoring system has been reported to have the greatest predictive power among all of the scoring systems. The APACHE II system has the added advantage that the score can be determined at any time and updated continuously with changes in the clinical situation. However, these scoring systems are only moderately accurate in assessing disease severity in individual patients. In a direct comparison of the Ranson score and the APACHE III score, a more sophisticated system than the APACHE II, the Ranson score was quite predictive of eventual outcome. Certain individual components of the Ranson score, including base deficit and blood urea nitrogen increase, proved particularly predictive.[86]

A CT-based severity index has been developed, with a score of 7 or greater implying acute pancreatitis with morbidity and mortality.[87]

Management

Adequate fluid resuscitation is the most important component in the management of pancreatitis. Third-space fluid losses can be severe, and invasive methods to monitor fluid status should be used, including urinary catheterization and, in severe pancreatitis, central venous monitoring, measurement of pulmonary artery wedge pressure using a pulmonary artery catheter or noninvasive cardiac monitor, and monitoring of cardiac parameters. Intubation

with respiratory support should be performed expeditiously for patients with severe respiratory compromise. Patients with severe pancreatitis should be monitored in an ICU for the development of distant organ failure. Pain control is an important treatment component.

Bowel rest traditionally has been used to interrupt the progression of pancreatic injury. Total parenteral nutrition has been used to support patients with a course of pancreatitis exceeding 3 weeks. However, recently 3 randomized controlled trials demonstrated the safety and feasibility of enteral feeding. These studies noted that enteral feeds were safer and were associated with fewer infectious complications and decreased expense.[88-90] Distal enteral feeding can also be achieved through the use of nasojejunal tubes, although their routine use in lieu of gastric feeds remains controversial.

Early endoscopic retrograde cholangiopancreatography may benefit patients who develop obstructive jaundice or cholangitis secondary to gallstone pancreatitis.[91] However, routine endoscopic retrograde cholangiopancreatography has no role in the management of pancreatitis, as this procedure has been associated with increased complication rates.[92]

Antibiotic prophylaxis for sterile pancreatic necrosis has been a topic of much clinical debate. Early studies suggested no benefit of prophylactic antibiotic therapy; however, recent data demonstrate that prophylactic antibiotic treatment can decrease the rate of pancreatic infection and may decrease overall mortality. A meta-analysis of 8 randomized controlled trials found a reduction in overall mortality in a subgroup of patients with severe pancreatitis when administered broad-spectrum antibiotics that could penetrate pancreatic tissue.[93] A Cochrane review of patients with CT-proven pancreatic necrosis demonstrated a decreased risk of pancreatic infection and mortality with antibiotic prophylaxis; however, the results of this analysis were greatly skewed by a dominant study.[94] Hence, antibiotic prophylaxis with an agent with good pancreatic tissue penetration (imipenem and cilastatin, third-generation cephalosporins, piperacillin, fluoroquinolones with metronidazole) in patients with documented pancreatic necrosis has become widespread practice. Recent evidence suggests that this benefit may be limited to the prophylactic use of imipenem.[95] However, a multicenter, prospective, double-blind, placebo-controlled study evaluating meropenem versus placebo in necrotizing pancreatitis demonstrated no significant difference in the incidence of infection, mortality, or need for surgical intervention. Hence, this remains an area of controversy and active study.[96]

Complications of Acute Pancreatitis

Infected Necrosis

It is reported that 30% to 70% of patients who develop necrotizing pancreatitis develop a pancreatic superinfection. Diagnosis of pancreatic infection is established using cultures of fluid aspirates through CT-guided fine-needle aspirates or tissue samples obtained during surgery. Radiological findings of gas in the pancreas are also highly suggestive of infection. Hence, CT-guided fine-needle aspiration is recommended for patients whose clinical course suggests infection or who fail to improve despite aggressive supportive measures.

Mortality rates for infected pancreatic necrosis range from 10% to 20%.[82] The treatment for infected pancreatic necrosis remains surgical debridement. Outcomes are better if surgery can be delayed until after 3 weeks following disease onset to allow for organization of necrotic pancreatic tissue. The procedure of choice is a necrosectomy, which is performed by debriding nonviable pancreatic tissue and avoiding anatomic pancreatic resections. Necrosectomy can be accompanied by closed drainage in which packing and drains are placed at the time of surgery and gradually withdrawn postoperatively. Necrosectomy with open packing followed by planned, staged relaparotomy every 2 to 4 days to allow for continued debridement of nonviable pancreatic tissue and packing change can be performed. Another surgical option is necrosectomy with continuous lavage whereby drains left at the time of surgery are continuously irrigated postoperatively until the effluent becomes clear and patients demonstrate clinical improvement. Any surgical debridement of the pancreas can be fraught with severe, life-threatening bleeding due to the massive retroperitoneal response and should be performed only by surgeons with experience in this area.

Recently, percutaneous, endoscopic, and minimally invasive techniques have been reported to treat pancreatic necrosis.[96] Endoscopic access through the stomach and serial irrigation and laparoscopic retroperitoneal exposure with pancreatic debridement have been reported. However, incomplete debridement remains a concern with these newer techniques, and no randomized trials have been performed comparing these new modalities to traditional open techniques. Other endoscopic techniques with evacuation of peripancreatic collections are becoming more popular as adjuncts to percutaneous drainage.[97] In the future, minimally invasive techniques will undoubtedly play an increasing role, but appropriate patient selection will be an important factor in outcomes.

Although in the past, surgical debridement was recommended for patients with sterile necrosis and absent infection, recent data show that nonoperative management of these patients can yield favorable outcomes.[98,99]

Pseudocysts

Pseudocysts are fluid collections lined by a rim of fibrous granulation tissue that develop in approximately 10% of patients who develop acute pancreatitis. Pseudocysts are distinguished from true pancreatic cysts by the absence of an epithelial lining. The majority of pseudocysts can resolve spontaneously; however, they also have the potential to cause local compressive symptoms leading to gastric outlet obstruction and obstructive jaundice. Pseudocysts can become secondarily infected, can bleed, or can rupture.

Pancreatic pseudocysts should be distinguished from cystic neoplasms of the pancreas. CT can identify radiographic features suggestive of neoplastic cysts, such as the presence of numerous small cysts. Endoscopic ultrasound with cyst fluid sampling is an important diagnostic tool in the differentiation of pseudocysts and neoplasms. Pseudocyst contents are high in amylase and lack mucin or glycogen, which are found in mucinous and serous cystic pancreatic lesions.

The presence of symptoms related to pseudocysts warrants intervention. Symptoms may be related to direct compression by the pseudocyst or may be secondary to an infected or bleeding cyst. In the past, indications for intervention in asymptomatic pseudocysts included pseudocysts larger than 6 cm and cysts that failed to decrease in size over a 6-week period. However, recent evidence suggests that even larger pseudocysts may resolve spontaneously. Intervention in asymptomatic pseudocysts remains an area of controversy.

The current options for cyst drainage include percutaneous drainage, internal drainage either endoscopically or surgically, or surgical resection. Endoscopic retrograde cholangiopancreatography to evaluate for ductal communication is important because these patients are at high risk of developing pancreatic fistulae if percutaneous drainage is undertaken. Internal drainage options include cystogastrostomy, cystoduodenostomy, or cystojejunostomy with a Roux loop of jejunum. Internal drainage can be accomplished endoscopically if anatomically feasible; however, open surgical drainage remains the gold standard treatment. Operative drainage should be delayed a minimum of 6 weeks following the inciting episode of pancreatitis to allow for cyst wall maturation. Recurrence

rates for pseudocysts are approximately 10%.

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CHAPTER 30

Abdominal Problems in the Intensive Care Unit

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Key words: diarrhea, *Clostridium difficile*, constipation, acute mesenteric ischemia, acalculous cholecystitis, abdominal compartment syndrome

Abdominal problems are common among patients in the ICU; some require surgical intervention, whereas others are treated non-operatively. Patients may present to the ICU with abdominal problems or may develop such problems as a consequence of other diseases or as a complication of therapeutic intervention. The diagnosis of abdominal complaints in the ICU is marked with difficulty; communication with the patient is impaired by sedation or the presence of an endotracheal tube, while paralysis may mask the more common physical findings. Extra-abdominal processes may mimic some of the signs and symptoms of abdominal abnormalities, and factors that assume significant importance in the evaluation of an otherwise healthy patient may not be relevant in the ICU. Other abdominal complications have subtle presentations that may be missed in the myriad of information associated with the care of a critically unwell patient.

A thorough description of all abdominal diseases and problems encountered in the ICU is beyond the scope of this chapter. Instead, the chapter is limited to a review of recent literature concerning problems that, if missed, may result in significant morbidity or mortality.

DIARRHEA

Definition

Diarrhea is a frequent problem in critically ill patients, affecting up to 90% of

certain ICU populations. The World Health Organization defines diarrhea as 3 or more liquid or unformed stools per day.

Approach to Diagnosis

Diarrhea increases patient discomfort, damages skin, and can have an adverse effect on nutrition and hydration. Wounds and femoral catheters in proximity are at risk of fecal contamination. The multitude of causes mandates a logical approach to diagnosis and treatment. The first step is to determine the presence of preexisting factors that may contribute to diarrhea (**Table 1**). In the ICU, infectious causes of diarrhea are less common than noninfectious causes but remain a major concern; infectious diarrhea is typically more severe and has an increased likelihood of causing complications such as electrolyte abnormalities or dehydration. In addition, the causative agent may be transmitted between patients and healthcare workers. Enteric feeds should not be stopped or delayed in a patient with diarrhea.

Table 1. Patient Factors Predisposing to Diarrhea

Inflammatory bowel disease
Prior surgery
Gastrectomy
Vagotomy
Small bowel resection
Endocrine dysfunction
Adrenal insufficiency
Hyperthyroidism
Hypothyroidism
Diabetes mellitus
Radiation
Malignancy
Colon cancer
Paraneoplastic syndromes

Infectious Diarrhea

Infectious causes should be considered when diarrhea is associated with blood or mucus in the stool, vomiting, severe abdominal pain, or fever. Causes of infectious diarrhea are listed in **Table 2**. Parasitic gastrointestinal infections, such as *Giardia lamblia* and *Cryptosporidium*, represent a significant portion of diarrhea cases in the developing world. Stool should be sent for microscopy, culture, and sensitivity and should be tested specifically for *Clostridium difficile* (as detailed below). Examination for ova, cysts, and parasites may be warranted depending on local prevalence or relevant travel history. Antibiotic therapy

should be aimed toward the suspected organism. Empirical vancomycin, while effective, likely contributes to the emergence of vancomycin-resistant enterococci.

Table 2. Causes of Diarrhea

Infectious	Small bowel bacterial overgrowth
Clostridium difficile	Blind loop syndrome
Salmonella	Motility disorders
Shigella	Short bowel syndrome
Campylobacter	Medications
Escherichia coli	Sorbitol
Vibrio cholerae	Magnesium
Giardia lamblia	Digoxin
Cryptosporidium	Propranolol
Rotavirus	Enteric feeds
Norovirus	Hyperosmolar solutions
Fecal impaction with overflow	Insufficient fiber
Pancreatic insufficiency	

Noninfectious Diarrhea

If stool culture proves negative but microscopy demonstrates the presence of red and white blood cells, consideration should be given to ischemia, malignancy, or inflammatory bowel disease.

If stool microscopy, culture, and sensitivity are negative, diarrhea may be due to osmotic shifts or malabsorption. Osmotic diarrhea can be caused by hyperosmolar enteric feeds or infected formula, both of which are less common in today's era of isotonic feeds supplied in sealed containers. Use of low-fiber formulas can decrease colonic commensal bacteria, which normally contribute to stool bulk and absorb colonic water, and the absence of these bacteria may result in diarrhea. Osmotic diarrhea also can be precipitated by medication containing magnesium or sorbitol (such as sucralfate and theophylline). Treatment of osmotic diarrhea entails removing predisposing medications, adding fiber to the diet, and altering the delivery timing and osmolarity of enteric formulas.

Pancreatic insufficiency may be present in both acute and chronic pancreatitis and responds to administration of pancreatic enzymes. Small bowel dysfunction may result from bacterial overgrowth in blind-loop syndrome; from altered transit in diabetic autonomic neuropathy, scleroderma, and other motility disorders; or from short bowel syndrome. Stool fat collection and oral D-xylose tests may help in the differentiation between pancreatic and small bowel disease.

Codeine phosphate, loperamide, or other agents that reduce bowel motility can be used to treat diarrhea once an infective cause has been excluded.

CLOSTRIDIUM DIFFICILE COLITIS

C difficile is an anaerobic, spore-forming, gram-positive bacillus that has emerged as a major enteric pathogen with a worldwide distribution. Transmission is by heat-, acid-, and antibiotic-resistant spores. In the absence of an intact fecal microbiome and its associated barrier properties, *C difficile* colonizes the large intestine. Factors that disrupt the fecal microbiome are the major risks for development of *C difficile* infection, with the most important factor being antibiotic therapy (**Table 3**). Colonization may be asymptomatic, but in susceptible patients the toxins that *C difficile* elaborates (TcdA and TcdB) cause colonocyte death, loss of intestinal barrier function, and subsequent neutrophilic colitis. Since the early 2000s, infection with the BI/NAP1/027 strain of *C difficile* has become more frequent. This isolate demonstrates more fluoroquinolone resistance, more efficient spore production, and significantly higher toxin production, all of which contribute to a higher rate of severe *C difficile* colitis and a mortality rate up to 3 times higher than that of less virulent strains.

Table 3. Risk Factors for *Clostridium difficile* Infection

Antibiotic use (ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones most frequently)
Age >65 years
Inflammatory bowel disease
Organ transplantation
Chemotherapy
Chronic kidney disease
Immunodeficiency

Diagnosis

C difficile infection is diagnosed by the presence of signs and symptoms of colitis and microbiological evidence of *C difficile* or its toxins in stool (**Table 4**).

Table 4. Clinical Pictures Consistent With *Clostridium difficile* Infection

Sign or	Definition

Symptom	
Diarrhea	Stool frequency >3 per 24 hours
Ileus	Vomiting and absence of stool with radiological signs of bowel distension
Toxic megacolon	Radiological evidence of colon distension (>6 cm transverse width of colon) plus signs of a severe systemic inflammatory response

Stool culture is the most sensitive test but has a clinically impractical turnaround time. The diagnosis can be made by testing for *C difficile* products in stool; enzyme immunoassay tests (cell culture cytotoxic assay, *C difficile* common antigen [glutamate dehydrogenase], or *C difficile* toxins A, B, or C) or nucleic acid amplification tests (16S RNA, toxin genes, or glutamate dehydrogenase genes) may be used. The DNA-based tests may allow identification of the specific strain, which has therapeutic implications, but their high sensitivity may also detect clinically insignificant infections. A 2-stage approach with a positive first test confirmed by a different second test has been advocated, but in clinical practice, a symptomatic patient with a positive test for *C difficile* should be treated promptly.

There is no utility to repeat testing prior to resolution of the diarrhea, and posttreatment testing to confirm eradication also has no role. Colonoscopic findings of pseudo membranes are pathognomonic for *C difficile* colitis, and biopsy may be useful in cases that are difficult to diagnose.

Treatment

The inciting antimicrobial agent should be discontinued at the earliest opportunity. Antiperistalsis agents should be avoided, as they may precipitate toxic megacolon. Empirical antibiotics should be instituted, either oral metronidazole or oral vancomycin. More recent studies suggest superiority of vancomycin. Fidaxomicin is a newer antibiotic approved for treatment of *C difficile* colitis. Although markedly more expensive, fidaxomicin is as effective as vancomycin and is associated with a lower recurrence rate in non-BI/NAP1/027 strain *C difficile* infections. Intravenous vancomycin does not reach significant intraluminal concentrations and should not be used. The duration of treatment should be 10 to 14 days.

At present, insufficient evidence is available to support the routine use of probiotics, intravenous immunoglobulin, toxin-binding resins or polymers, or

monoclonal antibodies.

Severe disease is defined as an episode of *C difficile* infection associated with severe colitis or with a complicated disease course, with systemic toxin effects (eg, low albumin, acute kidney injury, or systemic inflammatory response) or shock. Vancomycin is the recommended antibiotic for severe *C difficile* infection.

An episode of recurrence should be treated similarly to the initial episode. A second recurrence should be treated with pulsed or tapered vancomycin or with fidaxomicin. Fecal microbial transplantation has also been shown to be effective.

Patients with *C difficile* colitis should be nursed with contact precautions, and hand hygiene with soap and water (as opposed to alcohol) should be emphasized. Contact precautions should be observed for the duration of the diarrhea. Environmental sources of *C difficile* should be identified, and chlorine-containing cleaning agents should be used for environmental contamination. There is little utility in screening healthcare workers or the environment for *C difficile*, and treatment of asymptomatic carriers is not recommended.

Surgical Intervention

Patients who fail to respond to medical therapy or who progress to the development of shock, megacolon, or perforation should be evaluated for surgical intervention. A serum lactate concentration greater than 5 mmol/L or a white blood cell count approaching 50 is associated with significant mortality and should also prompt surgical evaluation. Earlier colectomy is associated with improved survival.

The standard operation is subtotal colectomy with formation of an end ileostomy. Alternatively, creation of a loop ileostomy with high-volume colonic lavage and vancomycin instillation through the ileostomy has been shown to reduce mortality and morbidity while sparing the colon in selected patients.

CONSTIPATION

Constipation in the ICU setting can be defined as the failure of the bowel to open for 3 consecutive days. As well as potentially indicating a serious underlying disease, the presence of constipation may inappropriately delay institution of enteric feeding and subsequently delay patient progress. **Table 5** lists causes of constipation.

Table 5. Causes of Constipation

Underlying bowel condition
Mechanical obstruction
Electrolyte abnormalities and related dysmotility
Opiate administration
Low-fiber enteric feed formula
Dehydration
Immobility
Previous long-term laxative use
Lack of privacy, distress

Bowel Management Protocols

The use of an evidence-based bowel management protocol in an ICU may decrease the number of patients experiencing diarrhea and constipation and allow the implementation of early enteral nutrition with its attendant benefits. A closed feeding system delivering a standard, isotonic enteric formula should be used, including fiber to promote normal colonic commensal functioning. Enteric feeds are rarely the cause of diarrhea, so they should not be stopped if diarrhea develops. If no other cause for the diarrhea is found, a reevaluation of the choice of enteric formula is appropriate.

Stool softeners (sodium docusate) or stimulant laxatives (senna) should be prescribed for all patients receiving enteric feeds. Osmotic laxatives (polyethylene glycol) and enemas should be used if constipation develops. Antimotility drugs, such as loperamide, should be used only in cases of uncomplicated diarrhea associated with severe colic or dehydration and are contraindicated in infectious diarrhea.

ACUTE ACALCULOUS CHOLECYSTITIS

Acute acalculous cholecystitis (AAC) is defined as acute inflammation of the gallbladder in the absence of cholelithiasis. AAC can be complicated by the development of gangrene, perforation, and empyema of the gallbladder and has a significant mortality, up to 90% if the diagnosis is delayed. AAC occurs in up to 0.4% of critically ill patients. The diagnosis may be challenging because patients are often sedated, intubated, or unconscious, making interrogation and

examination difficult. The clinical findings of AAC—right upper quadrant pain, fever, leukocytosis, and abnormal liver function tests—are nonspecific, and so a high index of suspicion for AAC should be maintained in critically ill patients whose condition worsens without explanation. Risk factors for AAC are listed in **Table 6**.

Table 6. Risk Factors for the Development of Acute Acalculous Cholecystitis

Trauma (especially if >12 units of packed red blood cells transfused or Injury Severity Score >12)
Recent surgery
Shock
Sepsis
Critical illness (any patient requiring ICU admission)
Total parenteral nutrition
Prolonged fasting

Diagnosis

Given the difficulties inherent in clinical evaluation of a critically ill patient, the diagnosis of AAC rests on imaging. Ultrasound (US), computed tomography (CT), and hepatobiliary iminodiacetic acid (HIDA) scan are commonly used. None of these modalities has sufficient sensitivity or specificity to make the diagnosis of AAC in isolation: Combination with other imaging modalities may be useful, and the overall clinical picture should always be considered.

Ultrasound

US is a useful modality because the study is performed in real-time, may be done at the bedside, and is easily repeatable. The diagnosis is made by the presence of 2 major criteria, or 1 major criterion and 2 minor criteria (**Table 7**). Although US has been shown to have a very high specificity, ranging from 89% to 100%, sensitivity is low; many ICU patients have US abnormalities of the gallbladder without having AAC (**Figure 1**).

Table 7. Ultrasound Diagnosis of Acute Acalculous Cholecystitis

Major criteria	>3.5 mm of wall thickening Pericholecystic fluid or subserosal edema

	Intramural gas Sloughed mucosa
Minor criteria	Echogenic bile (sludge) Gallbladder hydrops (distension >8 cm longitudinally or >5 cm transversely with clear fluid)

Figure 1. Ultrasound image of acute acalculous cholecystitis demonstrating a thickened gallbladder wall (between crosses) as well as wall edema (marked with white arrow)

Computed Tomography

CT requires transportation of the patient, which may not be feasible in the ICU setting. Nevertheless, CT may be useful in cases where AAC is possible but other causes of intra-abdominal abnormality are under consideration. When CT is used, the diagnosis is made by the presence of 2 major criteria, or 1 major criterion and 2 minor criteria (**Table 8**).

Table 8. Computed Tomography Diagnosis of Acute Acalculous Cholecystitis

Major criteria	>3 mm of wall thickening Pericholecystic fluid or subserosal edema Intramural gas

	Sloughed mucosa
Minor criteria	Hyperdense bile (sludge) Subjective distension

Hepatobiliary Iminodiacetic Acid Scan

HIDA radionucleotide cholescintigraphy is a nuclear medicine study involving intravenous administration of radio-labeled technetium that is subsequently excreted into the biliary tract. If the gallbladder is not visualized, the study is considered positive for cystic duct obstruction, most likely due to cholecystitis. HIDA scan has been shown to have a sensitivity of 91% in the diagnosis of AAC, but the main drawback is the requirement for transport of a critically ill patient to the nuclear medicine suite.

Treatment

The two prevailing treatment modalities for AAC are cholecystostomy (drainage of the gallbladder) and cholecystectomy (removal of the gallbladder).

Cholecystostomy can be performed under CT or US guidance. Cholecystostomy can provide definitive treatment for AAC but it is more commonly used as a bridge to cholecystectomy by improving the patient's condition and allowing time for optimization prior to surgery. Cholecystectomy is the definitive therapy and can be performed both laparoscopically and open. Cholecystostomy will not improve the patient's condition in the presence of gallbladder ischemia—cholecystectomy is mandated in such cases.

When AAC is highly suspected but imaging modalities have been negative, either empirical cholecystostomy or diagnostic laparoscopy has some utility.

ACUTE MESENTERIC ISCHEMIA

Causes and Risk Factors

Acute mesenteric ischemia can result from occlusive or nonocclusive obstruction of either the arterial inflow or venous outflow of the intestines. The most common cause is embolism of the superior mesenteric artery. This is a highly morbid condition, and autopsy studies suggest mortality rates of at least 90%; in only 33% of the cases in these studies was mesenteric ischemia considered.

Thrombosis of the arterial inflow occurs less frequently—15% to 30% of cases—and tends to be superimposed on existing atherosclerotic disease. Venous thrombosis is associated with multiple risk factors (**Table 9**).

Mesenteric ischemia may also occur in the absence of arterial or venous occlusion as a result of splanchnic hypoperfusion or vasoconstriction (nonocclusive mesenteric ischemia). This tends to occur in elderly patients with significant atherosclerotic disease.

Table 9. Frequency of Acute Mesenteric Ischemia and Associated Risk Factors

Arterial embolism (30%-50%)	Atrial fibrillation Myocardial infarction with wall motion abnormalities and associated thrombus Structural heart defects (right-to-left shunts)
Arterial thrombosis (15%-30%)	Atherosclerotic disease
Venous thrombosis (5%)	Cirrhosis or portal hypertension Pancreatitis Hypercoagulable states Oral contraceptive use Malignancy Factor V Leiden, protein C or S resistance, prothrombin 20,210 mutation Recent surgery Previous deep venous thrombosis or pulmonary embolism
Nonocclusive ischemia (20%-30%)	Atherosclerotic disease Advanced age Vasopressor use Low-flow states Sepsis Myocardial infarction or heart failure Arrhythmias Intermittent hemodialysis

Cocaine use

Vasoactive Therapies

Dopamine has historically been infused at low rates (<5μg/kg/min) with the intention of improving splanchnic circulation. Low-dose dopamine has little effect, however, and may in fact decrease gut mucosal blood flow. Dobutamine usually increases splanchnic circulation, but this effect may depend on the adequacy of baseline splanchnic perfusion. The effects of vasopressin on the visceral microcirculation remain unclear.

As with other vascular beds, the splanchnic circulation has a significant degree of local autoregulation. The interaction between the systemic effects of vasoactive therapies and local autoregulation remains unclear. More important than the specific vasoactive therapy used is the need to ensure volume resuscitation; the presence of appropriate intravascular volume is required to maintain adequate splanchnic blood flow and avoid visceral ischemia.

Diagnosis

Clinical Presentation

The signs and symptoms of acute mesenteric ischemia are nonspecific. Until there is transmural involvement of the bowel wall, there is minimal tenderness to palpation. The classic description of pain out of proportion to physical examination findings is absent in 20% to 25% of patients, and acute mesenteric ischemia may be mistaken for more common conditions. Patients may have abdominal pain, distension, diarrhea, lower gastrointestinal bleeding, or the signs and symptoms of sepsis. This diagnosis can be difficult to make in an awake, cooperative patient, and it is monumentally challenging in the typical ICU patient.

Laboratory Studies

The laboratory findings in acute mesenteric ischemia tend to be nonspecific and insensitive. Hemoconcentration, leukocytosis, an elevated anion gap acidosis, or lactic acidosis may be present. A patient may also have elevated levels of amylase, aspartate aminotransferase, or lactate dehydrogenase.

Radiological Studies

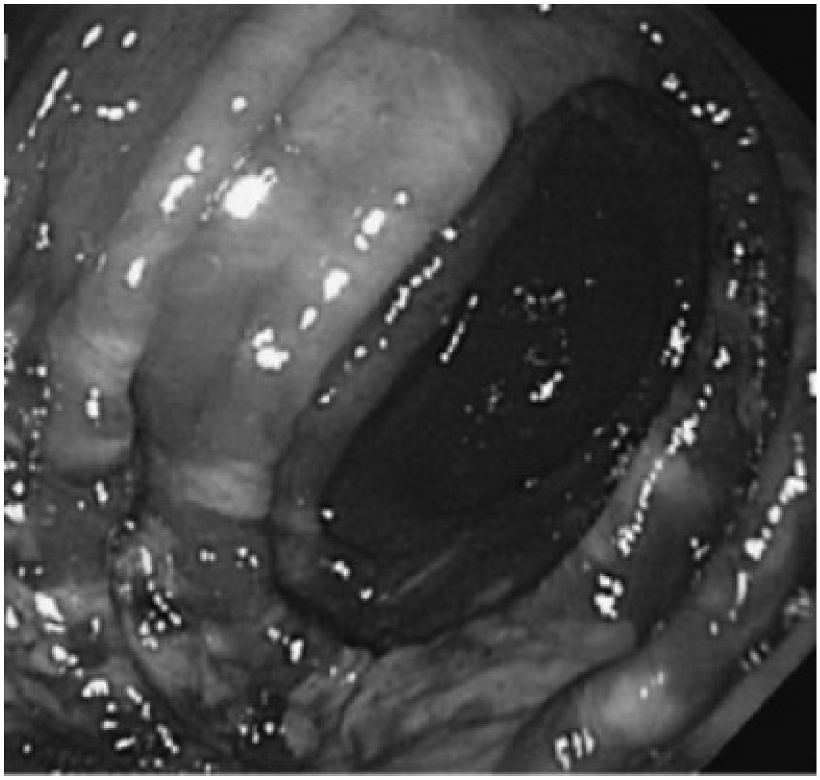
Up to 25% of patients with acute mesenteric ischemia may demonstrate normal plain abdominal radiographs. Ileus may be seen early in the process, whereas bowel wall edema (or thumbprinting) or pneumatosis intestinalis may be present in advanced cases.

Contrast studies are contraindicated in suspected mesenteric ischemia as they may interfere with subsequent angiography. US studies have limited utility; duplex images can be obtained only of the proximal superior mesenteric artery, but emboli tend to impact distally and bowel gas can easily obscure the mesenteric vessels. Visceral duplex is a highly technical, highly operator-dependent study.

Computed tomography angiography (CTA) is the study of choice in suspected mesenteric ischemia. Imaging of the mesenteric vessels is possible with concurrent bowel evaluation and exclusion of other abdominal disorders. The use of multidetector systems and biphasic imaging protocols (CT performed in both the arterial phase and delayed phase of contrast circulation) can improve detection, with a sensitivity of 93% and a specificity of 100% (**Figures 2 and 3**).

Figure 2. Computed tomography image demonstrating thrombus within the superior mesenteric artery (indicated with white arrow)

Figure 3. Colonoscopic images in a patient with ischemic colon, demonstrating inflammation of the transverse colon



The diagnosis of acute mesenteric ischemia hinges on high clinical suspicion in a patient with known risk factors. Rapid diagnosis is essential given the associated risk of mortality; thus, early and liberal use of CTA or angiography is encouraged.

Treatment

The goal of treatment is to restore intestinal perfusion. Fluid resuscitation with crystalloid solutions should be instituted early. Broad-spectrum antibiotic therapy limits the likelihood of bacterial translocation and subsequent sepsis. If no contraindications are present, systemic anticoagulation should begin in order to limit thrombus propagation. Unfractionated heparin infusion is preferred, because this allows rapid reversal should surgery become necessary. Heparin infusion should be restarted after surgery.

Patients with acute mesenteric ischemia often demonstrate significant fluid sequestration and may require significant volumes of fluid; bladder pressure monitoring may be warranted to recognize the development of abdominal compartment syndrome (ACS). Use of vasopressors should be judicious as they may cause visceral vasospasm and worsen ischemia in marginal bowel. Prior to the administration of any vasopressor, adequate filling pressures in the right side

of the heart must be present, and pure α-adrenergic agents should be avoided. Despite being supplanted in diagnosis by CTA, angiography is a vital component of initial therapy, allowing directed instillation of vasodilators, angioplasty and stenting, aspiration embolectomy, and thrombolysis.

Surgical Therapy

If the patient is suspected of having infarcted or perforated bowel, immediate surgical exploration is indicated. In cases of thrombosis or embolus in the mesenteric vessels, surgical embolectomy or thrombectomy is required. Combined procedures involving open thromboembolectomy or bypass and endovascular stenting are possible.

Acute Mesenteric Ischemia Following Cardiac Surgery

Mesenteric ischemia is an uncommon but serious complication of cardiac surgery, with a mortality of more than 50%. The patients at highest risk are those who require continued pharmacological and mechanical support after prolonged cardiopulmonary bypass **(Table 10)**. CT and US studies can be helpful in determining the patency of the mesenteric arteries but are inadequate in assessing flow in nonocclusive mesenteric ischemia. Thus, bowel viability is often assessed in these patients by exploratory laparotomy.

Table 10. Risk Factors and Predictors for Mesenteric Ischemia After Cardiac Surgery

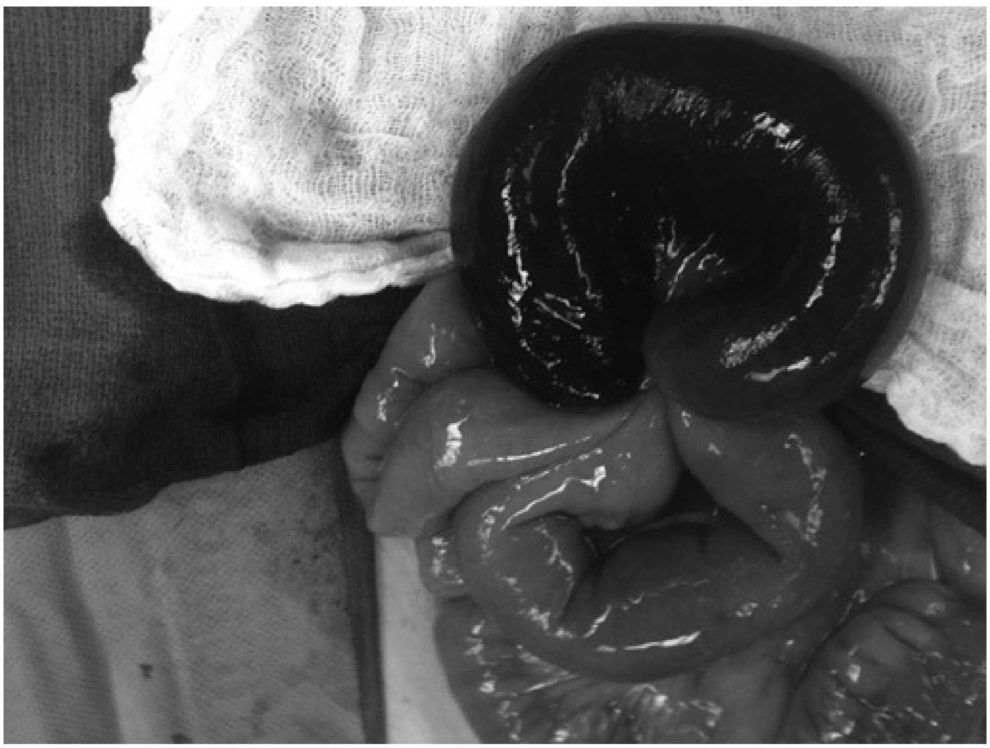
Presence of comorbid peripheral vascular disease
Triple-vessel coronary disease
Duration of cardiopulmonary bypass
Postoperative blood transfusions
Use of vasopressors
Use of intra-aortic balloon pump

Acute Mesenteric Ischemia Following Aortic Surgery

Mesenteric ischemia occurs frequently after aortic surgery and is present in up to 30% of elective open aortic aneurysm repairs. The mortality rate is approximately 90% if infarction develops. The risk factors are less well defined than in cardiac surgery. Presumed causes include interruption of the inferior mesenteric artery and transient occlusion of the celiac and superior mesenteric

arteries by clamping, hypotension, reperfusion injury, or embolization. The reported rate of visceral ischemia after endovascular repairs is lower than after open operations, but the causative factors in the endovascular setting are less well understood, although microembolization may be an important factor. Because collateral flow may be present and the progression from ischemia to infarction is less inevitable, endoscopic evaluation of the colon may be a useful adjunct to nonoperative therapy. A high index of suspicion for ischemia must be maintained, and prompt intervention is warranted in those patients who fail to improve (**Figure 4**).

Figure 4. Findings at time of operation in a patient with superior mesenteric artery emboli – the small bowel is non-viable.



ABDOMINAL COMPARTMENT SYNDROME

Elevation in intra-abdominal pressure (IAP) was once considered exclusive to trauma patients but is now recognized as a significant cause of organ dysfunction in all patient populations, one that can lead to organ failure, morbidity, and mortality.

Definitions

The abdomen can be considered a closed system, located within the rigid bony walls of the pelvis and spine as well as flexible walls consisting of the abdominal wall and diaphragm. The pressure within the abdomen reflects the relationship between its contents and the flexibility of its walls. The IAP is defined as the steady-state pressure concealed within the abdominal cavity. Normal IAP in healthy adults ranges from subatmospheric to 0 mm Hg, but IAP may be elevated in elderly or obese people.

Normal IAP in critically ill adults is 5 to 7 mm Hg. IAP elevations exist in a spectrum from mild elevations with no clinical impact to significant elevations with adverse effects on all systems. Pathological intra-abdominal hypertension (IAH) is defined as a sustained or repeated elevation in IAP of 12 mm Hg or higher. ACS is defined as a sustained IAP greater than 20 mm Hg associated with new organ dysfunction or failure. Failure to recognize and treat ACS is fatal, but timely intervention results in improvement in organ function and improved overall patient survival. Causes and risk factors for IAH and ACS are listed in **Table 11**.

Table 11. Causes and Risk Factors for Development of Intra-abdominal Hypertension and Abdominal Compartment Syndrom

Diminished abdominal wall compliance	Capillary leak or fluid resuscitation
Abdominal surgery	Acidosis
Major burns	Damage control laparotomy
Prone positioning	Hypothermia
Increased intraluminal contents	Massive fluid resuscitation
Gastroparesis	Massive transfusion
Ileus	Others
Colonic pseudo obstruction	Coagulopathy
Volvulus	Massive incisional hernia repair
Increased intra-abdominal contents	Mechanical ventilation, positive end-expiratory pressure >10 cm H_2O
Acute pancreatitis	Obesity or elevated body mass index
Hemoperitoneum	Peritonitis
Pneumoperitoneum	Pneumonia
Intra-abdominal infection or abscess	Sepsis
Intra-abdominal or retroperitoneal	Shock or hypotension

tumors

Liver dysfunction with ascites

Peritoneal dialysis

Grading and Classification

IAH can be graded on the basis of IAP value (**Table 12**). ACS, however, should be considered as an all-or-nothing phenomenon.

Primary ACS is IAH that has developed from an intra-abdominal cause. Secondary ACS is due to an extra-abdominal cause such as sepsis and the resultant capillary leak or a condition requiring massive resuscitation. Patients may have primary and secondary ACS concurrently. Recurrent ACS is an acute elevation in IAP in a patient recovering from IAH or ACS and may occur even in the presence of an open abdomen.

Table 12. Grading of Intra-abdominal Hypertension (Modified Burch Classification)

Grade	Intra-abdominal Pressure
I	12-15 mm Hg
II	16-20 mm Hg
III	21-25 mm Hg
IV	>25 mm Hg

Measurement

Physical examination and clinical determination of the presence of a "tense" abdomen offer no utility in the prediction of IAP. A variety of techniques can be used to measure IAP, both direct (puncture of the abdominal wall) and indirect (transduction of bladder, gastric, or colonic pressures). The accepted standard is bladder pressure monitoring. This technique is simple and cost-effective and has been widely adopted. A pressure transducer is connected to the sampling port of a Foley catheter. Since the abdominal contents are primarily fluid in character and are noncompressive, a pressure measurement at one point—in this case, in the bladder—should represent pressure throughout the abdomen. Intravesicular pressures should be measured at end expiration with the patient completely supine. Efforts should be made to ensure that there is no abdominal muscle

contraction, although paralysis is not always necessary. The transducer should be zeroed at the level of the midaxillary line. The bladder is instilled with no more than 25 mL of sterile saline, and the measurement takes place 30 to 60 seconds after instillation to allow detrusor muscle relaxation.

Effects

IAH can result in elevation of the diaphragm, with consequent reduction in functional residual capacity and thoracic compliance. Peak inspiratory pressure and pulmonary vascular resistance are elevated. A vicious cycle develops: Increased levels of positive end-expiratory pressure are required to maintain oxygenation and alveolar recruitment but can impair the arterial inflow and venous outflow of the abdomen, elevating IAP.

Increased IAP also results in elevations in central venous pressure and systemic vascular resistance. Cardiac output is impaired due to effects on venous return, and hypovolemia exacerbates this effect.

Renal dysfunction is common in ACS due to direct compression of the renal parenchyma as well as compression of the renal veins and inferior vena cava. A subsequent reduction in renal blood flow and glomerular filtration rate occurs. Oliguria is often the earliest sign of ACS. Changes in IAP have a greater effect on renal function than do changes in mean arterial pressure.

As ACS develops, intra-abdominal visceral perfusion decreases. In animal models, increased IAP is associated with decreased gastric and ileal blood flow, decreased oxygen levels in small bowel tissue, altered hepatic arterial and portal venous flow, impaired hepatic energy production, and increased bacterial translocation.

Elevated IAP is also associated with elevated intracranial pressure and decreased cerebral perfusion pressure, likely due to impaired jugular venous outflow.

Management

Given the number of conditions that predispose to IAH, ACS may occur in a disparate patient population. The fundamental treatment concepts, listed next, remain valid across all patient populations.

1. Serial monitoring of IAP

2. Optimization of systemic perfusion and organ function
3. Use of appropriate medical therapies to reduce IAP
4. Prompt surgical evaluation and decompression in patients with ACS or refractory IAH

Sedation, Analgesia, and Paralysis

Increased thoracoabdominal muscle tone may result from pain, agitation, ventilator dyssynchrony, and increased work of breathing, with subsequent elevation in IAP. Sedation and analgesia may thus reduce IAP, and neuromuscular blockade may improve abdominal wall compliance.

Body Positioning

Elevation of the patient's head reduces the risk of aspiration pneumonia but can increase IAP. Prone positioning can also significantly increase IAP.

Evacuation of Intraluminal Contents

Air and fluid within hollow viscera can raise IAP. Nasogastric drainage, rectal drainage, or endoscopic decompression may reduce IAP, as can the administration of prokinetic agents. Neostigmine may be useful in cases of colonic pseudo obstruction. Enteral nutrition should be minimized or discontinued.

Fluid Balance

Excessive fluid resuscitation can cause IAH and is a major factor in the development of secondary ACS. Resuscitation volumes should be carefully monitored at all points during the patient's care to avoid overresuscitation, and consideration should be given to the use of colloids or hypertonic crystalloid solutions. Patients with IAH who develop oliguria should be evaluated for early intermittent dialysis or continuous hemofiltration rather than subjected to fluid challenges. Diuretic therapy may be useful in mobilizing third-space fluid if hemodynamic status permits.

Evacuation of Intra-abdominal Space-Occupying Lesions

Abdominal US or CT may be used to identify intra-abdominal space-occupying lesions, such as abscesses, ascites, or other fluid collections, which may be

amenable to percutaneous drainage or evacuation.

Abdominal Decompression

Surgical decompression of the abdomen remains the standard treatment for patients with ACS or refractory IAH. Presumptive decompression—“leaving the abdomen open”—in patients undergoing laparotomy who are at risk for development of ACS is an option, but the open abdomen itself is associated with significant morbidity and mortality. Decompression in established ACS should not be delayed, and it may be performed in the ICU if necessary. Abrupt hypotension may develop, due to the sudden decrease in systemic vascular resistance or the release of vasoactive metabolites from ischemic tissue. Volume resuscitation should be judicious.

The resultant open abdomen should be covered by some form of temporary abdominal closure. Temporary abdominal closure may be achieved with homemade systems or commercially available products. All closure systems generally involve the application of negative pressure to the open abdomen, the use of an intra-abdominal drape to prevent adherence of the viscera to the abdominal wall, and the application of suction to maintain medial traction on the fascia as well as remove fluid from the abdomen.

The longer the abdomen is open, the greater the potential for the development of complications and subsequent morbidity. Definitive abdominal closure or coverage should be pursued at the earliest opportunity. Primary closure of the fascia is the standard, but if the patient remains critically ill, the exposed viscera can be covered with a split-thickness skin graft, or the skin only can be closed and the fascia left open. Fascial closure can then be attempted 9 to 12 months later.

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CHAPTER 31

Coagulopathies, Thrombotic Disorders, and Blood Component Therapy

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Key words: disseminated intravascular coagulation, blood product, transfusion, prothrombin complex concentrates, massive transfusion

This chapter addresses the myriad of coagulopathic states and thrombotic disorders that are commonly encountered in critical care. Coagulation abnormalities involve complex processes and can be congenital, iatrogenic, or products of disease or medication. The causes, diagnoses, and treatments of many of these abnormalities are addressed, and the chapter includes a discussion of modern blood component therapy and its complications.

COAGULATION OVERVIEW

Coagulation abnormalities are commonly encountered in the ICU.[1] Their management relies on a thorough understanding of the coagulation pathways and the ways in which they can be affected.

Separation of the intrinsic and extrinsic pathways allows the novice to learn the steps of coagulation in an orderly, stepwise fashion (**Figure 1**). However, in reality, the process is much more complex, with both coagulation and fibrinolysis occurring simultaneously. Current understanding of the intrinsic and extrinsic pathways includes the presence of significant cross-talk between the two, with factor VIIa of the extrinsic pathway crossing over to enhance activation of factors IX and XI of the intrinsic pathway. This underscores the central role that factor VII and tissue factor play in vivo.[2] Additionally, thrombin acts on several feedback loops to enhance upstream activation of the clotting cascade (**Figure 2**).

Figure 1. Coagulation cascade

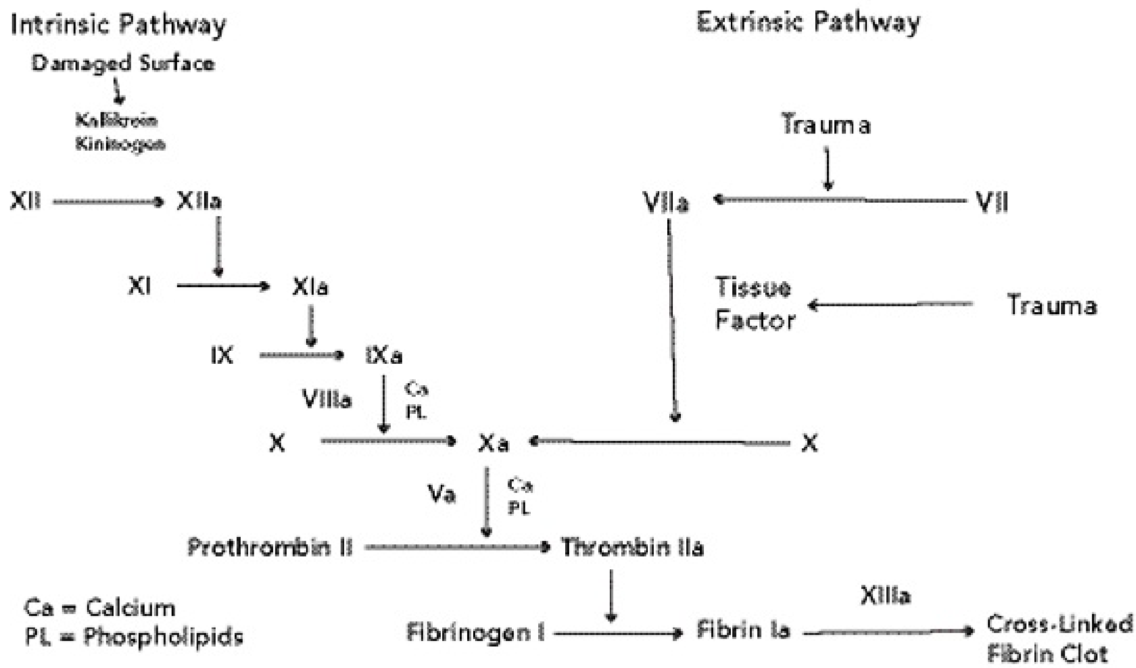
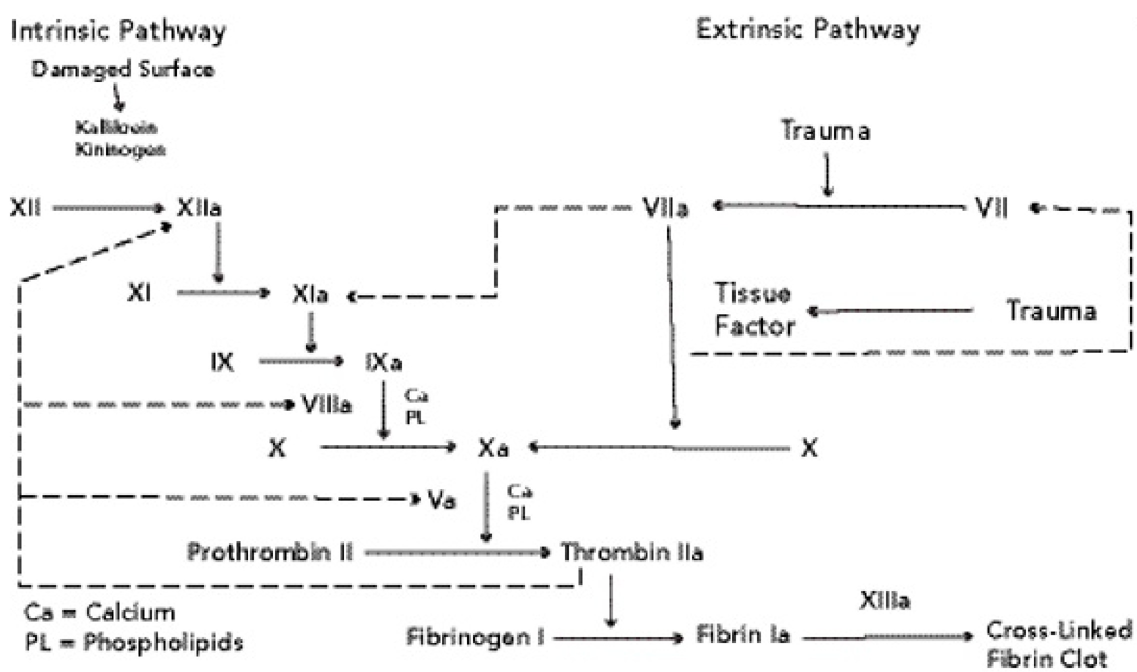


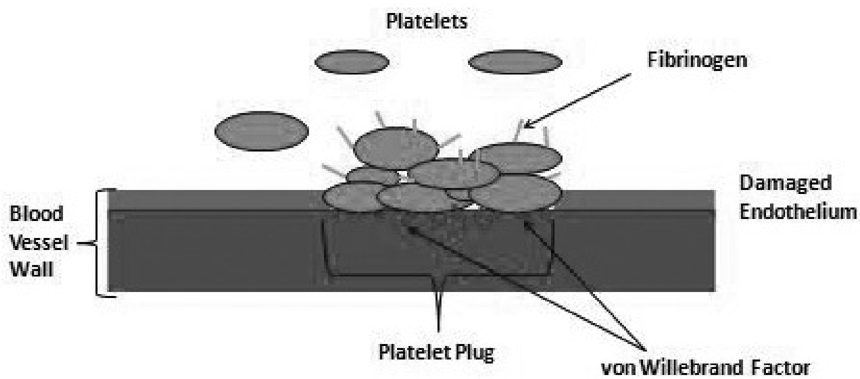
Figure 2. Modified coagulation cascade indicating points of cross-talk



The roles of the endothelium and of platelets are also of distinct importance. Platelets not only initiate the “platelet plug” but also bring specialized proteins to the site of injury. The platelet plug provides a surface for the creation of the

fibrin clot. Platelets bind to the damaged endothelium or exposed subendothelial matrix via a von Willebrand factor–mediated mechanism. This leads to further platelet activation, causing aggregation, adherence, vasoconstriction, and clot formation (**Figure 3**).[3]

Figure 3. Platelet plug formation



COAGULOPATHIES

History and Physical Examination

The majority of bleeding patients in the ICU can be quickly and accurately assessed with a thorough history and physical examination. A family history or personal history of excessive bleeding with previous minor procedures or trauma may reveal a genetic predisposition to bleeding. A meticulous review of a complete medication list may also reveal a previously overlooked cause of continued bleeding in the ICU. The clinician must consider severe liver disease or risk factors for cirrhosis (eg, alcohol consumption or history of hepatitis) and should assess elderly or debilitated individuals for malnourishment, which can lead to vitamin K deficiency.

Physical examination should be used to answer a few simple questions. Is the bleeding diffuse or localized? Inspection of mucosal membranes, IV insertion sites, or drainage tubes will help differentiate between the two. Is the bleeding mechanical or surgical in nature? Bleeding peptic ulcers, diverticular bleeding, or uncontrolled vessels in a postoperative patient all should lead to early involvement of a surgeon.

Physical examination can help diagnose specific medical conditions that contribute to coagulopathy. The abdominal examination may reveal signs of

portal hypertension, such as ascites and caput medusae. Splenomegaly can be associated with a variety of conditions that lead to bleeding. Physical findings such as the Grey-Turner sign or Cullen sign can indicate severe retroperitoneal bleeding.

Laboratory Examination

A basic set of coagulation parameters must be obtained in the assessment of a bleeding patient. This consists of international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet count, and fibrinogen level (**Table 1**). A note of caution is necessary when one orders these tests in ICU patients, whose samples are often drawn from indwelling catheters. These catheters may contain heparin as part of either the flush or the infusion. The aPTT is exquisitely sensitive to heparin and will be falsely prolonged if insufficient waste is withdrawn from an indwelling catheter prior to withdrawal of the sample. Most ICUs either use saline flushes exclusively or have nursing protocols in place to avoid heparin contamination of blood samples.

Table 1. Laboratory Findings of Common Coagulopathic States

Disseminated intravascular coagulation	Prolonged PT-INR, aPTT; decreased fibrinogen, platelets
Massive transfusion	Prolonged PT-INR, aPTT; decreased fibrinogen, platelets
Anticoagulant overdose	
Heparin	Prolonged aPTT; increased or decreased PT-INR
Warfarin	Prolonged PT-INR; prolonged aPTT (severe)
Thrombotic thrombocytopenic purpura	Decreased platelets; PT-INR, aPTT, fibrinogen generally normal; mild anemia
Hemolytic uremic syndrome	Hemolytic anemia; increased or decreased platelets; PT-INR, aPTT, fibrinogen generally normal

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

An isolated, elevated prothrombin time (PT)–INR level is commonly due to factor VII deficiency. In the critically ill, this is a common finding attributable to increased consumption of factor VII.[4] Elevation of both the PT-INR and aPTT

suggests multiple defects in coagulation or deficiency of factors II, V, and X. This laboratory pattern can also be seen with very low fibrinogen levels.

Specific Conditions

Warfarin

Warfarin, a commonly encountered medication in the critically ill population, is prescribed for a wide variety of conditions. Warfarin acts via competitive inhibition at the vitamin K receptor sites on factors II, VII, IX, and X. This leads to a depletion of the active forms of the vitamin K–dependent factors. Therefore, the INR must be carefully monitored to avoid excessive accumulation of the drug, which could result in life-threatening coagulopathy. Reversal of warfarin is often necessary in the ICU population. The rapidity of the reversal is based on the clinical needs of the individual patient. For elevated INR without clinical signs of hemorrhage, simply stopping the drug will cause a gradual normalization of the INR. Generally, 12 to 36 hours will be needed to see a resultant decrease in the INR.[5]

In cases where more rapid reversal of warfarin is indicated, vitamin K can be used.[6] Both oral and IV forms of vitamin K are effective. The oral route is generally slower but safer, because the IV form is associated with a small risk of anaphylaxis (3:10,000).[7] The oral route will take approximately 12 hours for onset of action, whereas the IV form takes only 4 hours (**Table 2**).[8]

Table 2. Vitamin K Dosing

International Normalized Ratio	Not Bleeding	Non–Life-Threatening Bleeding
2-3	Hold dose	2.5 mg of IV vitamin K
3-4.5	Hold dose	2.5 mg of IV vitamin K, consider FFP
4.5-10	1 mg of vitamin K by mouth	5 mg of IV vitamin K and FFP
>10	2.5 mg of vitamin K by mouth	10 mg of IV vitamin K and FFP

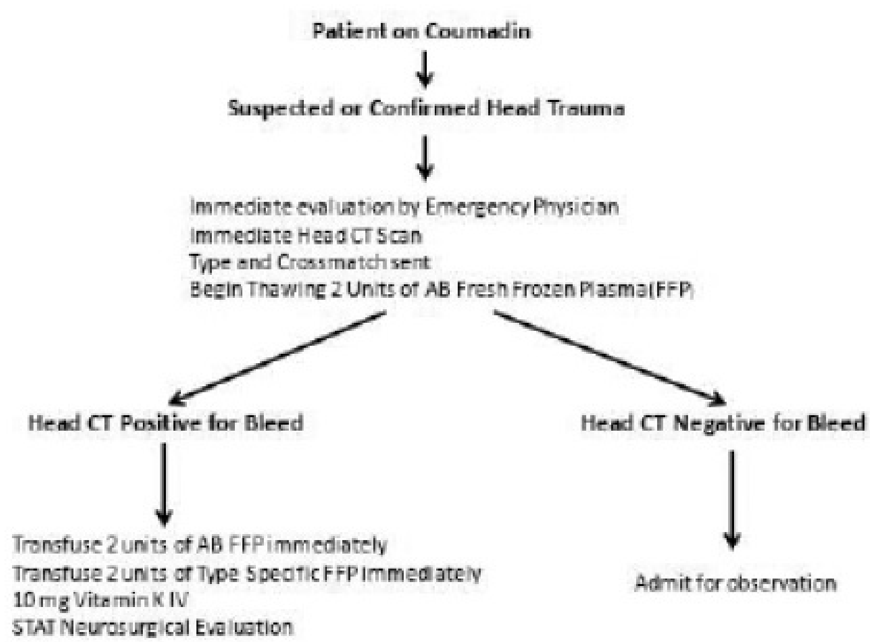
Abbreviation: FFP, fresh frozen plasma.

If the patient requires emergent reversal because of bleeding or urgent surgery, he or she should be given both IV vitamin K and fresh frozen plasma (FFP). One

unit of FFP will elevate coagulation factors by approximately 5%; therefore, large doses (4-5 U) may be necessary to reverse a significantly elevated INR. This volume of plasma infused rapidly may cause trauma-associated cardiac overload in susceptible patients.

Intracranial hemorrhage in patients receiving warfarin can have devastating consequences. These hemorrhages tend to expand rapidly due to anticoagulation, potentially resulting in bad outcomes. Intracranial hemorrhages can result from relatively minor trauma or can occur spontaneously because of warfarin-induced coagulopathy. Generally, reversal will be achieved with rapid administration of FFP and IV vitamin K. Recent studies show that in head trauma patients with warfarin-induced coagulopathy, institutional protocols that fully reverse coagulopathy with rapid administration of FFP and IV vitamin K result in decreased rates of intracranial hemorrhage progression and mortality (**Figure 4**).[9]

Figure 4. Beaumont Health coumadin-head injury protocol



Abbreviation: CT, computed tomography.

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Prothrombin complex concentrates (PCCs) are increasingly used for the effective reversal of warfarin-induced coagulopathy. Four-factor PCCs (factors II, VII, IX, and X) are now available in the United States. Administration of 4-factor PCCs has been shown to result in more rapid correction of coagulopathy than the use

of FFP and vitamin K in patients requiring emergent reversal of coumadin.[10] Patients who experience intracranial hemorrhage while receiving warfarin should be reversed in the most expeditious manner available at the individual institution, whether it is rapid administration of large amounts of FFP or administration of PCC (**Figure 5**).

Figure 5. Oregon Health and Science University prothrombin complex concentrate protocol for rapid warfarin reversal

- Patient receiving warfarin
- Life- or brain-threatening bleeding
- INR: 2-4
  25 U/kg not to exceed 2,500 U

  2.5 mg of vitamin K
- INR: 4-6
  35 U/kg not to exceed 3,500 U

  5 mg of vitamin K
- INR: >6
  50 U/kg not to exceed 5,000 U

  5-10 mg of vitamin K

Abbreviation: INR, international normalized ratio.

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Heparin

Unfractionated heparin (UH) has immediate effects on coagulation via its binding with antithrombin III (ATIII). This heparin-ATIII complex has a strong affinity for thrombin and results in inactivation of thrombin and inhibition of clot formation. UH will also directly inhibit activated factor X; however, this does not contribute significantly to the anticoagulation produced by administration of UH. In patients with a congenital deficiency of ATIII, it is difficult to achieve therapeutic aPTT despite administration of large doses of UH. In these patients, it becomes necessary to transfuse FFP simultaneously with UH in order to provide ATIII for the anticoagulation process.

The half-life of UH is relatively short (30-60 minutes). In most situations, UH anticoagulation can be passively reversed simply by stopping the UH infusion.

However, if the clinical scenario requires immediate normalization, protamine sulfate must be given. Protamine ionically binds to heparin, resulting in a complex with no anticoagulant activity. The dose of protamine is calculated based on the amount of heparin infused and the amount of time since heparin administration. The effect of protamine dosing should be confirmed with aPTT monitoring. The usual dose of protamine is 0.5 to 1 mg for every 100 U of heparin estimated to be circulating in the patient. Care should be taken with administration of protamine because side effects are commonly seen with rapid infusion, including hypotension and anaphylactoid reactions. Infusion should be performed over the course of 8 to 10 minutes.[11]

Low-molecular-weight heparin (LMWH) is commonly used in both inpatient and outpatient settings. This form of heparin works exclusively through inhibition of activated factor X. LMWH results in a more stable level of anticoagulation because of a longer half-life (3-5 hours) and is amenable to bolus therapy every 12 or 24 hours. Dosing of LMWH generally does not require monitoring because it does not produce consistent aPTT prolongation. LMWH is typically monitored by anti–factor Xa activity levels, but these have been shown to not correlate with subsequent thromboembolic events.[12] Reversal of LMWH is somewhat problematic. Protamine will not fully neutralize the effect of LMWH, and multiple doses may be necessary because of the longer half-life of LMWH.[13] Recombinant factor VII has been reported to stop bleeding associated with LMWH therapy but is not commonly used.[12]

Novel Oral Anticoagulants

The need for outpatient anticoagulation continues to increase. The drawbacks of food and drug interactions and the need for close laboratory monitoring associated with warfarin therapy have prompted the development of targeted antithrombotic medications. Three such medications are currently available and being used for the treatment of atrial fibrillation, deep vein thrombosis (DVT), and pulmonary embolism (PE) and the perioperative prophylaxis of VTE. Apixaban and rivaroxaban are both direct factor Xa inhibitors. Dabigatran etexilate (pro-drug) is converted to dabigatran after hepatic processing. This drug acts by directly inhibiting both free and clot-bound thrombin (factor IIa) and thus blocking the conversion of fibrinogen into fibrin.

By targeting specific clotting factors of the common pathway, these novel oral anticoagulants produce a stable anticoagulant effect without the need for close laboratory monitoring. Unfortunately for the intensivist faced with emergencies

or life-threatening bleeding, no means of reversal for these medications are widely available. The terminal half-life of all 3 drugs ranges from 4 to 17 hours, making reversal problematic in acute emergencies. Theoretically, PCCs, both activated and nonactivated, can be used in efforts to overwhelm the coagulation cascade and the effect of the drug at the common pathway. Additionally, hemodialysis has become part of many institutions' reversal pathways for dabigatran. This is a theoretically effective treatment because this drug has low protein binding and is amenable to elimination with hemodialysis. This is not the case for both apixaban and rivaroxaban, which are both highly protein bound drugs and are not cleared by hemodialysis.

In fall 2015, the US Food and Drug Administration granted accelerated approval to use idarucizumab as a reversal agent to dabigatran. Idarucizumab is a humanized monoclonal antibody fragment that binds strongly to dabigatran, thus inhibiting its binding to thrombin. Due to the accelerated approval process, idarucizumab has only 2 indications for use: (1) the need for emergency surgery or invasive procedures or (2) life-threatening or uncontrolled bleeding in a patient receiving dabigatran. Reversal is reportedly achieved in a matter of minutes to hours. Preliminary data show that 89% of patients achieved complete reversal by 4 hours. Thromboembolic events have been observed with the use of idarucizumab, and they require monitoring. Idarucizumab is not widely available at present, and full approval is contingent on the results of an ongoing cohort study.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC), a secondary complication of a primary medical condition, is one of the most serious hemostatic abnormalities faced by the intensivist. Many different conditions can be associated with the development of DIC (**Table 3**).

Table 3. Disease States Associated With Disseminated Intravascular Coagulation

Sepsis	Disseminated malignancy
Traumatic shock and hemorrhage	Hepatic dysfunction
Tissue necrosis and crush injuries	Penetrating brain injuries
Burns	Retained placenta
Fat emboli	Amniotic fluid embolism
	Eclampsia

DIC results from the inappropriate activation of thrombin generation. The end result is widespread conversion of fibrinogen to fibrin with resultant consumption of clotting factors and platelets. Eventually, this process can lead to significant bleeding as the consumption of platelets and factors outstrips their production. Fibrinolysis is initiated as a result of thrombin formation in DIC. The generated plasmin will break down fibrinogen and fibrin clots and inactivate several different coagulation factors as well as inhibit platelet activation. Severe bleeding from DIC is a result of 3 separate processes: thrombocytopenia, thrombin-induced factor consumption, and plasmin generation.

Thrombotic complications, which can occur in patients suffering from DIC, are due to the widespread formation of fibrin thrombi in the microcirculation. Renal failure, transient cerebral ischemia, pulmonary emboli, and acrocyanosis have all been attributed to microcirculatory ischemia seen in DIC.

Because DIC generates both bleeding and thrombotic complications, ICU patients with DIC will generally manifest 1 of 4 patterns of disease:

1. Asymptomatic DIC: Risk factors for these patients include sepsis and widespread cancer. Patients show laboratory evidence of DIC with thrombocytopenia (<100,000 platelet count, or >50% decrease from baseline), hypofibrinogenemia (<100 mg/dL, >50% decrease from baseline), elevated PT (>3 seconds prolongation), and increased d-dimer.[14] Asymptomatic patients will show no other signs but are at high risk for decompensation if the underlying disorder worsens.

2. Bleeding: The patient will present with diffuse bleeding from multiple sites, including IV insertion and mucosal membranes. As discussed above, the bleeding is due to the culmination of 3 separate processes.

3. Thrombosis: Isolated thrombosis is a rare presentation for a patient with DIC yet can occur despite aggressive activation of the coagulation cascade. Only 10% of patients will present this way, and thromboses tend to be venous rather than arterial.[15] Risk factors include trauma, malignancy, and pregnancy.

4. Purpura fulminans: This severe form of DIC is most often encountered after a viral or meningococcal infection. The associated skin lesions often begin

as painful red areas on the extremities that rapidly progress to full-thickness necrosis. In severe cases, these lesions can involve underlying tissue and lead to amputation. Treatment of purpura fulminans remains controversial, and many different therapies are used. Plasmapheresis, hemofiltration, and protein C concentrates have been used with modest success.[16,17]

Acquired Platelet Disorders

Uremia

Renal failure is commonly encountered in the ICU population, either as a preexisting comorbidity or as a result of the current illness. The resultant uremia is associated with an increased risk of bleeding, including subdural hemorrhage or gastrointestinal bleeding. This defect is not well understood but appears to be an impairment of the platelet–vessel wall interaction, likely due to an effect of uremia on von Willebrand factor. The impairment appears to be related to the severity of the patient's anemia.

The approach to a bleeding uremic patient should begin broadly, because many of these patients have been exposed to heparin during dialysis or have vitamin K deficiency. The intensivist must rule out these causes by checking PT-INR and aPTT values rather than assuming that the defect is due to uremia. Once other causes of bleeding have been eliminated, uremic bleeding can be treated effectively with hemodialysis. Additional pharmacological treatments include desmopressin or 1-deamino-8-D-arginine vasopressin (0.3µg/kg; maximum dose 21 mg). The effect lasts only 4 hours after infusion, and treatment should not be repeated more than once given the diminished response and the risk of tachyphylaxis. Desmopressin appears to act by increasing the plasma concentration of von Willebrand factor and improving platelet adhesion. Additionally, conjugated estrogens (10 mg every day) have been used effectively through an unknown mechanism. The benefit of estrogens is generally not seen for 3 to 5 days, but dosing can be repeated without diminished effectiveness.

Antiplatelet Agents

Aspirin is an effective antiplatelet agent and is commonly prescribed to patients with coronary and cerebrovascular artery disease. Aspirin acts by irreversibly inhibiting platelet cyclooxygenase. This will inhibit platelet aggregation for the life of the platelet, generally 8 to 9 days. It is preferable to delay elective surgeries until 7 days after the discontinuation of aspirin. In the case of

emergency bleeding or need for high-risk invasive procedures, platelet transfusions can be given to ameliorate the effect of aspirin. Appropriate dosing of platelets and an effective method of determining adequacy of reversal have yet to be determined. In these scenarios, 1-deamino-8-D-arginine vasopressin has been used effectively.[18]

The thienopyridines, the most commonly prescribed being clopidogrel, also irreversibly inhibit platelet function for the lifespan of the platelet. This drug acts by binding to the P2Y12 adenosine diphosphate receptor,[19] leading to interference with platelet aggregation and fibrin cross-linking. The risk of bleeding in a patient receiving clopidogrel alone is equivalent to that of aspirin; however, these drugs are often prescribed in conjunction, leading to a 20% to 100% higher risk of bleeding compared with that seen with either agent alone.[20] No pharmacological reversal is available for clopidogrel. Platelet transfusion may be beneficial in severely bleeding patients.

Elective surgical procedures should be delayed at least 7 days from the last dose of clopidogrel to lessen bleeding complications. Discontinuation of clopidogrel in patients who have had recent placement of drug-eluting coronary stents puts these patients at high risk for acute thrombosis, which carries a significant mortality.[21]

Congenital Platelet Disorders

A few hereditary disorders are occasionally encountered in the ICU patient. Although rare, these disorders bear mentioning and should be suspected if the patient shows signs of platelet dysfunction without more common risk factors or medication exposures. Glanzmann thrombasthenia, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, and Gray platelet disorder can cause platelet dysfunction by various mechanisms and ultimately lead to bleeding.

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) do not cause coagulation disorders but do result in microvascular thrombosis and microangiopathic disease, leading to end-organ dysfunction. Symptoms often include thrombocytopenia, neurological symptoms, fever, renal dysfunction, and microangiopathic hemolytic anemia. Only approximately 40% of patients with TTP-HUS will exhibit the pentad of symptoms, but nearly 75%

will show evidence of a triad, including microangiopathic hemolytic anemia, thrombocytopenia, and neurological symptoms.

HUS is most often encountered in children. It generally has a prodrome of fevers and bloody diarrhea. *Escherichia coli* (O157:H7) or Shiga toxin is often the cause of endemic cases of HUS. TTP is likely due to either the absence of or the inhibition of a von Willebrand factor–cleaving protease. This results in the circulation of abnormally large von Willebrand factor complexes, which cause spontaneous platelet aggregation and adhesion to the endothelium. Sporadic cases of TTP-HUS are most often associated with medication exposures, including cyclosporine-tacrolimus, mitomycin C, and ticlopidine.[22] Bone marrow transplantation, both autologous and allogeneic, can be complicated by TTP-HUS at a rate of 5% to 15%.[23]

Treatment for TTP is plasma exchange; however, mortality remains nearly 20%.[24] Steroids are also used to further suppress the presumed autoimmune origin of TTP. They should be continued through full recovery to avoid relapse. Platelet transfusion is best avoided unless the patient shows signs of severe bleeding. HUS is treated with supportive care only, including renal replacement therapy. Plasma exchange has not been shown to be of benefit in HUS.

HELLP (Hemolysis, Elevated Liver Tests, Low Platelets)

Pregnant patients who are critically ill with thrombocytopenia most commonly have the HELLP syndrome. Presentation usually occurs after 28 weeks of gestation in a patient with underlying preeclampsia of varying severity. The platelet count will decrease, followed by an elevation of liver enzymes. Peripheral smears of the patient's blood will reveal evidence of hemolysis (ie, schistocytes). Spontaneous hepatic hemorrhage may occur. Maternal death can result from this process and the fetus may become involved, with 30% suffering from thrombocytopenia. Most cases of HELLP will subside upon delivery of the child; however, in refractory cases, steroids and plasma exchange may be necessary to treat the mother.[25]

Hemophilia A and B

Hemophilia A is a sex-linked recessive coagulopathy caused by insufficient synthesis or defective synthesis of factor VIII. All ethnic groups are affected by this disease, and worldwide incidence is 1 per 5,000 to 7,000 live male births.[26] Hemophilia A presents with variable severity depending on the percentage of

factor VIII activity. Hemarthroses and hematomas are common manifestations of the disease. As factor VIII levels decline, the patient may suffer from spontaneous hemorrhages from mucosal membranes or in the retroperitoneum. Spontaneous intracranial hemorrhages are rarely seen. Treatment has traditionally relied on factor VIII replacement using plasma and cryoprecipitate. This requires large volumes of transfusions to maintain even minimal levels of factor VIII. Several lyophilized factor VIII concentrates are available as well as products from recombinant techniques. Both of these types of products are safe and are more effective than traditional methods in replacing factor VIII levels in patients with hemophilia A.[27]

Hemophilia B, which is clinically indistinguishable from hemophilia A, is also a sex-linked recessive coagulopathy. Factor IX levels are deficient. The incidence is less than that of hemophilia A, occurring in 1 of every 25,000 to 30,000 live male births. Severity of the disease depends on functional factor concentrations. Treatment is factor IX replacement. Factor IX concentrates are available and are generated from either plasma or recombinant techniques. These concentrates are the best treatment for hemophilia B but are costly. Older treatment options include the use of PCCs, but this carries the additional risk of thrombosis because other factors are present in these preparations. However, the currently available PCC products are balanced between procoagulant vitamin K–dependent factors and anticoagulant factors including antithrombin III, heparin, and proteins C, S, and Z.

Thrombotic Disorders

Traditional causes of hypercoagulability are included in the Virchow triad of hypercoagulable states, stasis, and endothelial injury. Critical care patients frequently have these risk factors and are at high risk for thrombosis. Critical illness or trauma commonly entails immobilization, which leads to stasis. Patients often have endothelial damage as a result of recent surgery or interventions (ie, central venous catheters, dialysis catheters, and arterial lines). Hypercoagulable states can result from a myriad of processes including tobacco use, disseminated cancer, pregnancy, drug exposures, and congenital disorders. These can be divided into acquired and congenital states (**Table 4**).

Table 4. Hypercoagulable States

Acquired Condition	Congenital Condition
Trauma	Factor V Leiden

Sepsis	Protein C deficiency
Heparin-induced thrombocytopenia	Protein S deficiency
Antiphospholipid syndrome	Antithrombin III deficiency
Pregnancy	
Estrogen replacement therapy	
Hyperhomocysteinemia	
Malignancies	

The following noncardiac thrombotic events are common in the ICU:

1. Stroke
2. TTP-HUS
3. Heparin-induced thrombocytopenia
4. DVT
5. PE

Approximately 10% of ICU patients will develop a DVT despite some form of thromboprophylaxis. Of these patients, 15% will develop a clinically significant PE.[28] Many of these events are preventable. Each ICU patient should be assessed for her or his risk of thrombosis and any contraindications to thromboprophylaxis and should be treated accordingly. Although no one regimen has established superiority, patients should be treated with mechanical thromboprophylaxis such as sequential compression devices during their ICU stay. Chemical thromboprophylaxis should be considered in all ICU patients when it is no longer contraindicated.

Congenital Hypercoagulable States

Factor V Leiden Deficiency

Factor V Leiden deficiency is a point mutation, Arg506Gln, on 1 allele of the gene for factor V. The resultant protein from this mutation is resistant to cleavage by protein C. This results in underregulation of the Xa-Va prothrombin complex and excessive thrombin formation. This mutation is one of the most common thrombophilic states. It is found in up to 20% of patients who present

with their first unprovoked or idiopathic DVT.[29]

The syndrome is autosomal dominant. Heterozygosity is common in Caucasians, being present in nearly 1 of 20 asymptomatic individuals; however, only 1 of 2,000 persons with only 1 allele will become symptomatic per year.[30] Homozygosity confers a much higher risk of thrombotic events, affecting nearly 1 in 100 patients per year.

Protein C and Protein S Deficiencies

Both protein C and protein S act as anticoagulants by inhibiting factor V. Deficiencies in levels of either can lead to a prothrombotic state.[31] Heterozygosity for protein C deficiency is found in 1 in 500 of the general population and in 4% of patients experiencing their first DVT. Homozygosity of protein C deficiency produces a condition known as *neonatal purpura fulminans* and is not consistent with life. Patients who have protein S deficiency generally experience a less aggressive hypercoagulable state. Acquired protein C and S deficiencies can manifest in the setting of liver dysfunction and malnutrition, as they are both vitamin K–dependent factors.

Antithrombin III Deficiency

ATIII is the most powerful inhibitor of coagulation in the body. A deficiency of ATIII carries a much higher thrombotic risk than deficiencies of factor V Leiden, protein C, or protein S. The incidence of ATIII deficiency is relatively low, contributing to 5% of initial thromboses. Homozygosity of the genetic defect is not consistent with life. There are 2 variants of ATIII deficiency.[32] Type I is a reduction in the synthesis of ATIII, with 50% of normal antigen levels. Type II will result in functional deficiencies of ATIII, including binding of heparin, thrombin, or both.

Acquired Hypercoagulable States

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APAS) can cause significant confusion among clinicians. *Antiphospholipid antibody*, *anticardiolipin antibodies*, and *lupus anticoagulant* are terms that are dependent on the particular assay used for diagnosis. For the purposes of the intensivist, these can be viewed together as the APAS. This syndrome causes both arterial and venous thrombosis. Cerebral

infarction is not uncommon. The thrombophilic nature of APAS is not completely understood. Suspicion for APAS should be raised in the setting of associated clinical findings of venous and arterial thrombosis, idiopathic thrombocytopenic purpura, livedo reticularis, acrocyanosis, pulmonary hypertension, and possibly a history of obstetrical complications.

Heparin-Induced Thrombocytopenia

Although heparin-induced thrombocytopenia (HIT) is not classically described as a thrombophilia, it may manifest with thrombosis and is quite common in the ICU. HIT can be divided into 2 types. Type I, which is the focus here, is the more severe form. Type II HIT is a benign condition that entails an immediate and transient thrombocytopenia in response to heparin.[33] Type II HIT is generally mild, has no immunological basis, and does not lead to an increased risk of thrombosis.

HIT begins with formation of antibodies to heparin exposures of any type: IV heparin, subcutaneous heparin, UH, and even LMWH (albeit at significantly lower risk).[34] Upon subsequent exposure, these previously formed antibodies will bind the heparin–platelet factor-4 complex, causing platelet activation, release of microparticles, and thrombin generation. This process will lead to platelet consumption and eventually widespread venous and arterial thrombosis.

Diagnosis of HIT is generally based on suspicion, history of exposure, and clinical findings. Nonfunctional antibody assays are sensitive tests for HIT but lack specificity. Functional assays, like the serotonin release assay and the heparin-induced platelet aggregation assay, tend to lack sensitivity.[35] The serotonin release assay is the most reliable test overall,[36] but this test may not be readily available in all centers and its unavailability should not delay treatment if clinical concern is high.

HIT is treated by discontinuing all heparin-containing medications. In the critically ill, it is of utmost importance to ascertain that any commonly used devices that may be heparin bonded are discontinued and replaced with nonheparinized equivalents. This includes central venous catheters, renal replacement therapies, and cardiac assist devices. The next step in therapy is initiation of anticoagulation with a direct thrombin inhibitor such as argatroban or recombinant hirudin. Treatment length should be tailored to the clinical severity of the patient; however, it is generally recommended that the patient be therapeutically anticoagulated for 4 weeks even if there is no evidence of

thrombosis.[37]

BLOOD COMPONENT THERAPY AND MASSIVE TRANSFUSION

Blood products are obtained from donated whole blood. Approximately 11 million units of blood are donated each year in the United States. The basis of blood component therapy is to maximize the usefulness of such a limited resource. A blood bank can separate each unit of whole blood into 1 U of packed red blood cells (PRBCs), 1 U of platelets, and 1 U of FFP. Understanding the composition of these products and the expected effects that occur with transfusion is vital to the intensivist's management of many ICU issues and contributes to the stewardship of resources.

Components

Packed Red Blood Cells

Once the majority of plasma has been removed from a unit of whole blood, the remaining red blood cell mass is referred to as a unit of PRBCs. The hematocrit of a unit, which varies depending on the practices of the regional blood bank, generally ranges from 60% to 80%. The volume of a unit of PRBCs is approximately 340 mL. The unit is packaged with preservatives, a citrate-based anticoagulant, and usually a residual of 25 mL of plasma. Storage of PRBCs, often up to 42 days, will lead to rapid degradation of 2,3-diphosphoglycerate. This results in decreased off-loading of oxygen to the tissues despite an increase in oxygen-carrying capacity with recently transfused blood. This process is limited because 2,3-diphosphoglycerate levels are returned to normal at approximately 24 hours. Transfusion of blood older than 21 days has been associated with a decrease in tissue oxygenation.[38] However, two recent prospective randomized studies, one performed in critical care patients and one in cardiac patients, showed no increase in morbidity or mortality in patients transfused with older blood. These studies did not include patients who underwent massive transfusions.

The unit of PRBCs may undergo leukoreduction both before storage and again before transfusion in order to decrease rates of febrile reactions and human leukocyte antigen (HLA) alloimmunization. Irradiation may be performed to reduce contaminating lymphocytes and prevent transfusion-associated graft-vs-host disease. Washing of the PRBCs is rarely needed but is useful in cases of recurrent allergic reactions. In an average nonbleeding adult patient, transfusion

of 1 U of PRBCs will raise the hematocrit level by 3%.

Indications for transfusion of PRBCs in the ICU are changing rapidly. Increased awareness of the immunosuppressive effects of transfusions and subsequent effects on patient outcomes has led to a more restrictive transfusion practice. A large, prospective randomized trial by Hebert et al[39] showed no benefit of using a transfusion threshold of 10 g/dL versus 7 g/dL and suggested increased complications in the liberal transfusion group. A follow-up study that evaluated patients with cardiovascular disease also showed no benefit of a liberal transfusion policy.[40] Patients who were acutely bleeding and patients with active cardiac ischemia were excluded from these studies.

Platelets

Platelets can be prepared in 1 of 2 ways. They are either pooled from multiple random donors (ie, “six packs”) or produced from a single donor via apheresis (ie, 1 U of platelets). Both forms are equivalent in the amount of platelets that are transfused to the patient. The expected increase in platelet count from transfusion of a unit is 5,000 to 10,000 platelets/µL. Platelets may be “stunned” from storage and may require up to 4 hours in circulation to become fully functional. The volume of a unit of platelets is 300 mL. In the United States, platelets are suspended in a unit of plasma. Platelets have a shelf life of 5 days at 20°C (68°F) with constant agitation.

Many blood banks have begun providing only apheresed single-donor units of platelets. This allows for HLA matching. Patients can form antibodies to HLA antigens; these antibodies rapidly destroy subsequently transfused platelets with that HLA antigen. This becomes particularly problematic in patients who receive many transfusions over the course of their lives.[41] Rates of HLA immunization can range between 60% and 90% in patients with aplastic anemia or myelodysplasia or those receiving chemotherapy.

The risk of severe bleeding increases with profound thrombocytopenia. The risk of spontaneous intracranial hemorrhage is 0.76% per day when the platelet count is less than 1,000/µL. The risk of major bleeding is greatest when counts fall below 10,000/µL, with a risk of approximately 1.9% per day. In the same study, in patients with platelet levels between 10,000 and 20,000/µL, the risk of major bleeding was only 0.07% per day.[42] Indications for platelet transfusion include evidence of microvascular bleeding, surgical procedures in patients with platelet counts less than 50,000/µL, and thrombocytopenia entailing platelet counts less

than 10,000/µL. Platelets can be useful in treating bleeding patients who have seemingly adequate platelet counts and have received aspirin or clopidogrel.

Plasma

A unit of FFP is obtained from a single unit of whole blood. The volume of 1 U of FFP is 250 mL. FFP is stored frozen within 8 hours of donation and takes 20 to 30 minutes to thaw. It contains 60% to 80% of the normal levels of all coagulation factors and plasma proteins and can last up to 1 year if stored at –18°C (–0.4°F). Once the FFP has been thawed to 4°C (39.2°F), it can be stored for up to 24 hours. After 24 hours, FFP becomes thawed plasma, which can be stored up to 5 days. Factors V and VIII are labile and will deteriorate after 24 hours, but other factors are well-maintained. Thawed plasma expedites a balanced approach to massive transfusion.

FP 24 is plasma that is frozen between 8 and 24 hours after donation, allowing additional testing and fractionation of the product. FP 24 is used interchangeably with FFP but is not approved for the creation of thawed plasma. Liquid plasma is isolated from whole blood and is never frozen. By avoiding the freeze-thaw cycle of FFP, liquid plasma retains better factor function. Liquid plasma is approved for use when thawed at 4°C (39.2°F) for 26 days; it has excellent factor retention, except for factors V and VIII.

Transfusion of plasma should be ordered only in specific circumstances. Plasma is effective in the acute reversal of warfarin, in the treatment of coagulation factor deficiencies, as part of a massive transfusion, and in the treatment of DIC. Oftentimes, plasma is inappropriately transfused to treat patients with abnormal coagulation results. This exposes the patient to significant risk while providing little benefit, because plasma is ineffective in reversing minor elevations of INR (1.3-1.8) and because these patients frequently have normal clotting as measured by thrombelastography.[43]

Cryoprecipitate

Cryoprecipitate is the white precipitate formed when plasma is frozen and thawed. Storage is similar to FFP; however, once thawed, cryoprecipitate lasts only 4 hours. A unit is 15 mL of volume and contains 150 mg of fibrinogen and 80 to 100 U of factor VIII, in addition to von Willebrand factor and factor XIII. Cryoprecipitate is generally provided as a 5-U pool.

Cryoprecipitate can be used effectively to raise fibrinogen levels in patients with

DIC or as part of a massive transfusion. Because of the high levels of von Willebrand factor, cryoprecipitate has been used to treat bleeding in uremic patients. It was historically used for treatment of both hemophilia A and von Willebrand disease; however, cryoprecipitate has been largely replaced by more specific products as first-line therapy.

Risks and Complications of Transfusion

Transfusion-Transmitted Disease

In the United States, transmission of viral disease via transfusion of blood products is quite rare. Reductions in the risk of transfusion-transmitted disease are attributable to both improved donor screening and development of specific tests for these diseases (**Table 5**).

Table 5. Test for Common Transfusion-Transmitted Diseases

Test	Transfusion-Transmitted Disease
Antibodies to *Trypanosoma cruzi*	Chagas disease
HIV-1 and HIV-2 antibody	HIV/AIDS
Nucleic acid	HIV/AIDS and hepatitis C
Hepatitis C virus, anti–hepatitis C virus	Hepatitis C
Hepatitis B surface antigen	Hepatitis B
Hepatitis B core antibody	Hepatitis B
Syphilis serology	Syphilis
Human T-lymphotropic virus-1 and human T-lymphotropic virus-2 antibody	Human T-lymphotropic virus
Nucleic acid test for West Nile virus	West Nile virus

The risk of transmitting HIV is approximately 1 out of 2 to 4 million units of blood product transfused.[44] Hepatitis B and hepatitis C are commonly thought of as “classic” transfusion-transmitted diseases. The rates of transmission have been lowered significantly with better donor screening and the development of

diagnostic testing for the virus. Currently, the approximate risk is 1 out of every 1 to 2 million units transfused.[45] West Nile virus, syphilis, and babesiosis all can be transmitted via transfusions. Last, cytomegalovirus (CMV) transmission must be mentioned. In most patients, this results in no more than mild flu-like symptoms; however, CMV can cause devastating illness in immunocompromised patients. The CMV will lie latent in the leukocytes found in the donated blood. Two methods have been developed to reduce transmission of CMV. Most commonly, leukoreduction filters are used to remove the white blood cells from the blood before storage and transfusion. Additionally, the donor blood can be tested for antibodies to CMV, the presence of which indicates previous infection. New techniques are being developed for pathogen reduction of plasma.

Transfusion Reactions

Transfusion reactions can occur for a variety of reasons. Despite many built-in safety features in most institutions' transfusion protocols, human error is not a negligible factor in causing transfusion reactions. It is estimated that 1 in 15,000 to 19,000 U of product per year will be transfused to the incorrect patient. Rates of significant sequelae are much lower. This is likely attributable to the fact that randomly chosen blood will be compatible 64% of the time. Safety of transfusion has been greatly improved as a result of serological testing (**Table 6**).

Table 6. Rates of Compatibility With Serological Testing

ABO compatibility	99.4%
ABO and Rh compatibility	99.8%
ABO, Rh, and antibody screen	99.9%

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reaction is due to ABO incompatibility and was previously the most common cause of transfusion-related deaths. This reaction is almost exclusively a result of clerical errors. The estimated mortality is approximately 1 in 600,000 transfusions.[46] More than 50% of acute hemolytic transfusion reactions will result in death. The patient will initially exhibit fever, rigors, and IV site pain. This will quickly progress to hematuria, acute renal failure, and possibly DIC. Treatment includes the immediate cessation of the transfusion coupled with aggressive hydration.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is a form of noncardiogenic pulmonary edema and is now the most common cause of mortality after transfusion.[47] TRALI is believed to be due to the passive transfer of antileukocyte antibodies in donor plasma that destroy host granulocytes and activate the complement system, resulting in lung injury.[48] The process begins within 6 hours of transfusion, manifesting as fever, hypotension, and hypoxia. Treatment is supportive, with intubation and mechanical ventilation often required. Most patients will recover fully in 24 to 48 hours; however, 5% to 10% of TRALI episodes will result in death. The estimated risk of experiencing TRALI is 1 in 5,000 units transfused. The risk of TRALI is much higher after plasma transfusion from female donors who have been previously pregnant; this is caused by the production of HLA class I or II leukocyte antigens during pregnancy.[49] For this reason, many blood banks no longer transfuse plasma from females. The removal of female plasma from blood banks has been associated with a reduction in the incidence of TRALI.[50]

Bacterial Sepsis

Sepsis can occur as a result of transfusion. This is most often due to transfusion of platelets near the end of their shelf life. The patient will present with typical signs of sepsis, including fevers, rigors, and hypotension. Care is primarily supportive, but the clinician should culture both the patient and the bag of platelets and initiate broad-spectrum antibiotics for both gram-positive and gram-negative organisms. Bacterial sepsis occurs in 1 of every 15,000 U of platelets transfused.

Transfusion-Related Graft-vs-Host Disease

This complication is quite uncommon but can be lethal, with a mortality rate approximating 90%. Lymphocytes from the donor attack the recipient’s tissues, most often bone marrow. This disease generally occurs in already immunocompromised individuals: bone marrow transplant recipients, patients with leukemia, and patients with Hodgkin disease. Fever, rash, emesis, diarrhea, elevated liver function tests, and depressed blood cell counts form the constellation of signs and symptoms. Gamma irradiation of the blood products can eliminate this rare but deadly complication and should be used for all transfusions in at-risk individuals, including family-directed donations.

Minor Transfusion Reactions

Delayed hemolytic reactions occur in nearly 1 of 260,000 transfusions. The syndrome manifests with fever, jaundice, and anemia. It presents between 2 days and 3 weeks post transfusion. The recipient antibodies are responsible for attacking donated red blood cells. Treatment involves ensuring that subsequent transfusions are antigen negative.

Febrile nonhemolytic reaction is due to leukocyte debris and cytokines in the transfusion. A febrile reaction is defined as a body temperature increase of greater than 1°C. Patients who have suffered febrile reactions should be pretreated with acetaminophen for future transfusions. Leukoreduction filters should also be used. This complication is seen in up to 30% of platelet transfusions but only 0.5% to 1% of PRBC transfusions.

Volume overload or transfusion-associated cardiac overload occurs at a significant rate. Patients with a history of congestive heart failure and those who may be volume overloaded prior to transfusion are particularly susceptible. This can be treated with diuresis and supportive care.

Massive Transfusion and Acute Traumatic Coagulopathy

In the early 1980s, transfusion medicine made a transition from whole blood therapy to blood component therapy. Blood component therapy provides a number of advantages over whole blood transfusions. By separating blood into individual components, blood banks have been able to greatly extend storage times. Additionally, component transfusion allows physicians to transfuse only what is necessary for the patient’s particular problem. All of this has led to greater use of a limited resource. The unfortunate outcome of this transition, however, has been increased confusion in the management of the severely bleeding patient. Although most of the following discussion is based on experience with trauma patients, many of the concepts are applicable to any patient with life-threatening exsanguination (eg, gastrointestinal bleeding).

Protocols for massive transfusion that were developed after the implementation of blood component therapy were created without a comprehensive knowledge of the cause or the effect of coagulopathy in hemorrhaging trauma patients. Early protocols initiated resuscitation with large volumes of crystalloid and PRBCs. Coagulation factor depletion was presumed to be simply dilutional, and plasma and platelet transfusion was initiated only after 6 to 10 U of PRBCs had been

transfused. Trauma patients suffer from coagulation defects that are not explained by dilution alone. Shock and tissue injury can produce acute traumatic coagulopathy, which is mediated through the protein C pathway and is associated with a higher mortality.[51] Acute traumatic coagulopathy progresses through 3 separate temporal phases. Phase 1 is the immediate activation of multiple hemostatic pathways as a result of tissue damage, including fibrinolysis. Phase 2 results directly from resuscitative efforts: that is, dilution of hemostatic factors with crystalloid or PRBC transfusion. The prothrombotic state, which predisposes trauma patients to venous thromboembolism occurring during the postresuscitation period, constitutes phase 3.

Investigations have revealed that this coagulopathy is a complex interplay between temperature, tissue damage from the trauma itself, shock and acidosis, dilution of factors from resuscitation, and underlying diseases.[51] The formation of extravascular clot as well as thrombus formation leads to depletion of available coagulation factors and platelets. The loss of intravascular volume and circulating red blood cells due to acute hemorrhage disrupts axial blood flow through the vessel. Due to laminar flow dynamics, when a vessel is injured, red blood cells flow toward the center of a vessel while plasma and platelets flow closer to the walls. As the hematocrit level decreases and flow is disturbed, an inverse relationship occurs between in vitro bleeding time and hematocrit.[52]

Starling forces reverse in response to depletion of the intravascular space, leading to net migration of fluid from the interstitium back into the vasculature. This autodilution of coagulation factors is further worsened by aggressive use of crytalloid, colloid, or PRBC transfusion after blood loss. As noted in **Table 7**, even a balanced transfusion ratio (eg, a 1:1:1 ratio of plasma, platelets, and PRBCs) will deliver a dilute final product compared with the lost whole blood.

Immunological, hormonal, and cytokine response to tissue damage will affect the severity of acute traumatic coagulopathy. Epinephrine and vasopressin increase during shock, leading to endothelial cell activation. Vasopressin stimulates the release of tissue plasminogen activator and Weibel-Palade bodies from the endothelium. The Weibel-Palade bodies enhance platelet recruitment by releasing von Willebrand factor and exposing P-selectin. Cytokines, tumor necrosis factor, and interleukin 1 promote further endothelial cell activation when combined with ongoing hypoxia. This leads to a conversion from an antithrombotic to a prothrombotic state at the endothelial level, which causes DIC in inadequately resuscitated patients. Immune activation through the release of CD40 ligand from platelets can cause further endothelial cell activation and

platelet activation. Activation of the complement cascade releases damage-associated molecular proteins. Tissue damage is subsequently aggravated due to proteolytic degradation and oxidative stress, leading to further hemostatic activation.

Finally, the "lethal triad" of acidosis, hypothermia, and coagulopathy exacerbates acute traumatic coagulopathy. Obviously, transfusion protocols are aimed at avoiding coagulopathy in the bleeding patient by replacing both factors and platelets in addition to increasing oxygen-carrying capacity via PRBCs. However, no amount of factors or platelets will be effective if hypothermia or acidosis is also present. Hypothermia negatively affects platelet function, enhances fibrinolysis, and diminishes the efficiency of the coagulation cascade. Hypothermia is difficult to reverse, and the most effective course is prevention. This includes using active fluid warmers, minimizing exposure, and limiting operative times (ie, "damage control surgery"). Like all enzymatic reactions, the coagulation cascade functions ideally at a specific pH range. Significant acidosis not only inhibits these reactions but also affects other organ functions, like cardiac contractility, renal function, and cerebral function. Recognition of the interplay between all 3 parts of the lethal triad is the basis for care of the severely injured or bleeding patient. All efforts should be made to avoid hypothermia, maintain perfusion to avoid worsening acidosis, and aggressively replace both coagulation factors and platelets to avoid coagulopathy.

Traditionally, transfusion protocols have been based on response to laboratory testing (ie, transfusing FFP when the INR is >2.0 or transfusing platelets when counts fall below 75,000/μL). This reactive mode of transfusion medicine is not well suited to the management of an exsanguinating patient in whom empirical replacement of factors and platelets must accompany replacement of the red blood cell mass. Over the past 2 decades, retrospective data from both military and civilian experiences have indicated that more aggressive protocols of plasma and platelet transfusion confer a survival benefit for the seriously injured patient. Retrospective studies suggest that a 1:1:1 ratio of PRBCs, FFP, and platelets should be used for patients who are at risk for massive transfusion.[53,54] Interestingly, although this ratio of blood products seemingly re-creates whole blood, this is clearly a case where the whole is greater than the sum of its parts (**Table 7**).[55]

Table 7. Fresh Whole Blood Versus 1:1:1 Component Therapy

	Whole Blood	Component Therapy[a]
Volume	500 mL	660 mL

Hematocrit	38%-44%	29%
Platelets	150,000-400,000	87,000
Coagulation factor activity	100%	65%
Fibrinogen	1,500 mg	750 mg

[a]1 U of fresh frozen plasma, 1 U of packed red blood cells, "six-pack" platelets, and 10 U of cryoprecipitate.

Retrospective studies concerning transfusion ratios in patients undergoing massive transfusion suffer from survival bias, meaning that it is unclear whether patients survive because they receive a high ratio or whether they receive a high ratio because they survive. The Prospective Observational Multicenter Major Trauma Transfusion Trial (PROMMTT) revealed that less than 30% of patients received a 1:1:1 ratio of plasma, platelets, and PRBCs at the median time of death, which was 2.6 hours after admission.[56] Patients who underwent high-ratio transfusion were more likely to survive. In the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, severely injured patients were randomized to 1:1:1 versus 1:1:2 ratios of plasma, platelets, and PRBCs. Patients in the 1:1:1 group were more likely to be alive at 3 hours and less likely to die from exsanguination.[57] Most level I trauma centers in the United States currently use a ratio-based approach to massive transfusion.[58]

SUMMARY

Hemostasis and thrombosis are some of the most challenging disorders faced by an intensivist. Early recognition of these processes and prompt, appropriate intervention will improve outcomes. Blood transfusion practices are continually evolving. As our understanding of the complex processes of coagulopathy improves and as blood product substitutes are developed and become increasingly used, we can expect radical changes in the treatment of our most seriously injured patients.

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CHAPTER 32

Oncological Emergencies

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Key words: cancer, critically ill, emergency, ICU, oncology

According to the World Health Organization, cancer continues to be the leading cause of death in developed countries, with 14 million new cases and 8.2 million cancer-related deaths worldwide in 2012. The 5 leading types of cancer contributing to these deaths are lung, liver, stomach, colorectal, and breast cancer. Annual cancer cases are predicted to rise to 22 million over the next 2 decades.

As a result of recent developments in the treatment of cancer patients, we can expect to see more critically ill cancer patients admitted to ICU beds. Even though these patients come to require critical care for the same organ failures that noncancer patients encounter, patients with cancer often have unique circumstances that challenge the critical care team. Their critical illness may result from direct tumor-related effects, metabolic crises, cytopenias, direct effects of their treatment regimen, and exacerbations of preexisting comorbidities. These associations have been used to classify oncological emergencies accordingly. This chapter focuses on emergencies secondary to the neoplasm itself and emergencies related to treatment of the neoplasm, although many oncological emergencies also arise secondary to comorbidities.

DIRECT TUMOR-RELATED EFFECTS

Airway Emergencies and Malignant Airway Obstruction

Malignant tumors of the head and neck, respiratory tract, and mediastinum can often be associated with airway obstruction. When these lesions become symptomatic, they have high potential for an emergent presentation. Rapid

assessment must be performed, and the need for a lifesaving intervention such as intubation, therapeutic bronchoscopy, or emergent tracheostomy may develop quickly.

For many patients with malignant airway obstruction, symptoms will be exacerbated by the supine position. Patients with malignancies that cause extraluminal airway compression or intraluminal obstruction of the bronchial tree may present with postobstructive pneumonia or pneumonitis, lung collapse, or hemoptysis. Massive hemoptysis (>600 mL per 24 hours) usually requires immediate intubation for airway protection and either bronchoscopic intervention or an interventional radiology evaluation for potential embolization. Lesions causing invasion or extrinsic compression of the upper airway can cause stridor, drooling, and cyanosis, and some patients develop the "superior mediastinal syndrome" in which compression of the tracheobronchial tree, heart, and great vessels leads to stridor, orthopnea, cough, and severe dyspnea. Typically, exertional symptoms are not present until the trachea is narrowed to 8 mm or less, and nonexertional symptoms may not appear until the tracheal diameter is 5 mm or less.

Acute respiratory failure in the setting of a difficult airway is a true medical emergency, requiring the immediate attention of personnel with skill in advanced airway management techniques. Cancer patients have a high potential for difficult mask ventilation or intubation because of tumor location, radiation therapy, previous surgeries, or even coagulopathies that challenge the clinician's ability to establish an airway. When the clinician is presented with a patient who has malignant airway obstruction, the patient should be expeditiously transported to a controlled environment in which all potentially needed equipment is readily available. In addition to the anesthesiologist, a head and neck surgeon and a thoracic surgeon should be immediately available. Expertise with a variety of techniques to establish a patent airway is required. Patients should be allowed to spontaneously ventilate in a comfortable position (usually upright), and supplemental oxygen should be administered. Heliox, a mixture of 50% to 70% helium and 30% to 50% oxygen, should also be considered, because helium has a lower density than nitrogen and decreases the tendency for turbulent airflow, which can significantly improve a patient's work of breathing. Intravenous glucocorticoids and bronchodilator treatments may also be useful.

The intubation technique chosen depends on the location of the lesion. The patient with a severe proximal airway obstruction would likely be best served by a primary tracheostomy. Rigid bronchoscopy can be very helpful in unstable

situations and will allow for therapeutic interventions. Transnasal fiberoptic intubation is commonly used in the circumstances of a difficult airway related to malignant obstruction. This intubation can be accomplished in an awake patient who is sitting upright and receiving supplemental oxygen or a helium-oxygen mixture. This approach can present the specialist with challenges, such as distorted airway architecture, edema, blood, and secretions. Tumors, previous radiation, or previous surgery in the neck could affect the feasibility of surgical cricothyroidotomy if intubation is unsuccessful. Tumors in the central or distal airway usually require the involvement of the interventional pulmonary team to access the airway. Among the interventions available are photodynamic therapy, stent placement, electrocautery and argon plasma coagulation, cryotherapy, laser therapy, and rotating tip microdebrider.

Superior Vena Cava Syndrome

In the past, a significant majority of cases of superior vena cava syndrome were caused by malignancies, primarily non–small cell cancer, with typical progression of symptoms over weeks to months. Recently, the increased use of intravascular devices has led to an increase in the number of cases of the syndrome that are caused by thrombosis. Signs and symptoms lead to the diagnosis, and computed tomography (CT) can usually identify the cause. Obstruction of venous return leads to edema of the face, neck, and upper extremities as well as dyspnea. Elevation of the patient's head is a simple way to reduce hydrostatic pressure in the upper body. Glucocorticoids have been used to reduce the tumor burden in patients with lymphoma and thymomas. Patients may require chemotherapy, irradiation, or both, and vascular stents can be used to alleviate symptoms. These patients can also present significant challenges if endotracheal intubation becomes necessary.

Spinal Cord Compression

Spinal cord compression is one of the most devastating complications of malignancies, leading to significant declines in quality of life and predisposing patients to further complications, such as venous thrombosis, skin breakdown, respiratory compromise, and urinary obstruction. Metastatic spinal cord compression most commonly results from compression of the dural sac and spinal cord from extradural metastatic lesions, although direct extension by adjacent primary or metastatic disease or extension from subdural or intramedullary lesions can occur. Spinal cord compression occurs most often in

patients with carcinomas of lung, breast, or prostate.

Patients with spinal cord compression most commonly present with back or neck pain, which typically precedes the diagnosis by 2 to 5 months. The pain typically is progressive and is exacerbated by coughing or bending over, and it may have radicular features. Weakness is a development that commonly causes such patients to seek medical attention. Many initially describe “heaviness in the legs” or “clumsiness,” and the examiner discovers motor weakness.

When a cancer patient presents with back pain or weakness, the clinician should have a high index of suspicion for metastatic spinal cord compression. After a careful history and physical examination, imaging should be obtained. Magnetic resonance imaging (MRI) is usually the first test ordered when spinal cord compression is suspected. Ideally, this should be accomplished within 24 hours, and imaging of the whole spine should be obtained, as these patients may have multiple sites of spine metastasis. MRI is quite useful in ruling out metastatic disease as a cause of a patient’s symptoms.

Treatment should be initiated quickly, because patients with metastatic cord compression are at high risk for rapid deterioration. Corticosteroids, such as dexamethasone, are commonly used, because they decrease the edema that compresses nerves and blood vessels. Consultation with a radiation oncologist should be urgently obtained, as these lesions are often responsive to radiation therapy. Certain types of tumors may also be responsive to chemotherapy. Consultation with neurosurgery is also recommended, given that spinal decompression and stabilization may be necessary.

Intracranial Hypertension

Intracranial hypertension in the cancer patient can result from cytotoxic edema, acute hydrocephalus, or intracranial hemorrhage. Cytotoxic cerebral edema may be related to a primary central nervous system tumor or a metastatic lesion, whereas acute hydrocephalus usually represents obstruction of the normal cerebrospinal fluid flow in the brain. This may be related to local effects of primary or metastatic tumors or to intracranial hemorrhage. Intracranial hemorrhage has multiple potential causes.

A patient with intracranial hypertension typically will require placement of a monitor, usually an external ventricular drain, to measure intracranial pressure (ICP). Reasonable therapeutic goals include an ICP of less than 20 mm Hg and a

cerebral perfusion pressure of greater than 70 mm Hg. Analgesia and sedation are useful treatments for ICP elevation. Along with therapeutic drainage of cerebrospinal fluid via an external ventricular drain, osmotic therapy is recommended as a first-line treatment for ICP elevation. A common regimen consists of 20% mannitol administered every 4 to 6 hours, with doses from 0.5 to 1 g/kg. Hypertonic saline has also been shown to be safe and effective. Serum osmolality should be measured in patients receiving either hyperosmolar treatment, and the conventional practice is to hold further mannitol or hypertonic saline if the osmolality exceeds 310 mOsm/L. Hyperventilation is an effective way to lower ICP acutely, but its use is controversial because the mechanism of lowering intracranial blood volume involves vasoconstriction of intracerebral vessels, potentially impairing cerebral perfusion. Patients with refractory ICP elevation despite these measures may benefit from neuromuscular blockade or barbiturates. Barbiturates may be useful in patients with refractory intracranial hypertension who are considered to be salvageable. Hypotension is a significant side effect and should be anticipated when barbiturates are used. Patients receiving long-acting barbiturate infusions should be monitored with electroencephalography.

Cytotoxic Edema

Both primary and metastatic brain tumors are often associated with vasogenic edema, leading to dysfunction. Patients usually present with seizures, headaches, or new focal neurological deficits. CT findings will include distinct areas of contrast enhancement and associated edema, whereas MRI may reveal smaller lesions and may be more useful in determining size and location.

Treatment of symptomatic cerebral edema associated with neoplasm is often initially accomplished with corticosteroids, typically dexamethasone. Potential complications include hyperglycemia and psychosis, but patients usually respond quickly with at least some symptomatic improvement. Depending on the tumor type and location, as well as prior treatments, radiation or chemotherapy can be initiated. Although systemic chemotherapy usually has a modest role, radiation treatment, which can include whole brain irradiation or stereotactic radiosurgery, is more likely to be beneficial.

Intracranial Hemorrhage

The most significant risk factor for all patients with hemorrhagic stroke is hypertension, but patients with hematological malignancies, such as acute

myelogenous leukemia, lymphoma, or myeloma, are at increased risk, as is any patient with severe coagulopathy, which is a common complication of many cancer treatment regimens. As expected, patients with primary or metastatic brain tumors have increased risk of intracerebral hemorrhage, particularly late in the course of the disease. Lung cancer, melanoma, and germ cell tumors are associated specifically with increased risk of hemorrhagic stroke.

The patient presenting with an acute neurological deficit should have an emergent noncontrast CT scan of the brain to evaluate for intracranial hemorrhage. Urgent neurological and neurosurgical consultations should be obtained. Patients with intracranial hemorrhage are at considerable risk for progressive neurological deterioration due to expansion of the hemorrhage, increasing cerebral edema, or development of hydrocephalus, with the highest risk in the first 24 hours. The need for airway protection should be evaluated frequently, as many patients with supratentorial hemorrhage and most patients with brainstem or cerebellar hemorrhages will require intubation. Consequently, patients with intracranial hemorrhage should be admitted to an ICU. Neurosurgical evaluation is useful to determine whether evacuation of the hematoma is a reasonable consideration and for potential placement of a monitor to measure ICP.

Cancer patients with intracerebral hemorrhage frequently have associated coagulopathies, and these should be aggressively addressed and corrected. No data are available to strongly support a goal platelet count in these circumstances, but many neurosurgeons recommend correction to more than 100,000/mm^3 initially. Fresh frozen plasma, prothrombin complex concentrate, and vitamin K should be considered if the prothrombin time is prolonged.

Patients with intracerebral hemorrhage are at increased risk for seizures. Most of these events occur within the first 24 hours after the onset of symptoms. Seizure prophylaxis is of unclear benefit, but active seizures can lead to further neurological damage due to massive cerebral oxygen requirements and should be aggressively treated. Benzodiazepines followed by phenytoin are the usual treatments for seizures; barbiturates, propofol, and alternative antiepileptic medications can be considered in refractory cases.

Seizures

Seizures can occur as a direct complication of primary brain tumors or from metastatic disease to the brain. Patients with intracerebral hemorrhage also can

develop seizure activity, and seizure activity may result from syndromes such as posterior reversible encephalopathy syndrome, from the use of ifosfamide or intrathecal chemotherapy, or from other treatment-related neurotoxicity. Numerous antiepileptic drugs are available, although the newer-generation non–enzyme-inducing anticonvulsants, such as levetiracetam, lacosamide, or pregabalin, may be better tolerated and have fewer potential drug interactions than older medications such as phenytoin or valproate.

Cardiac Tamponade

Malignant pericardial effusions occur either due to excess fluid secretion from metastatic tumor nodules on the surface of the pericardium or due to obstruction of lymphatic drainage. Melanoma, lymphoma, leukemias, and gastrointestinal tumors are most frequently associated with malignant pericardial effusions.

Most pericardial effusions in cancer patients are asymptomatic. Symptomatic patients usually present with shortness of breath, orthopnea, or pleuritic chest pain, and physical examination findings may include jugular venous distention, tachycardia, hypotension, distant heart sounds, and peripheral edema. Pulsus paradoxus is a classic finding with tamponade, and an electrocardiogram may demonstrate low voltage, particularly in the anterior leads, as well as electrical alternans. The most useful diagnostic test to determine whether tamponade physiology exists is an echocardiogram. Echocardiography will demonstrate and quantify the effusion, will allow the clinician to evaluate the hemodynamic impact, and is useful to guide therapeutic drainage, if indicated.

Patients with tamponade physiology are most commonly treated with bedside ultrasound-guided pericardiocentesis with drainage catheter placement. If the pericardial fluid is not amenable to this procedure or is recurrent, a pleuropericardial window should be considered.

Hyperleukocytosis, Leukostasis, and Pseudohypoxemia

Hyperleukocytosis has been defined as a total white blood cell count greater than $50 \times 10^9/L$ in the setting of leukemia. Patients with hyperleukocytosis are at increased risk for leukostasis, which is characterized by symptoms of decreased tissue perfusion. This is considered a medical emergency and is most commonly seen in patients with acute or chronic myeloid leukemia. Tissue hypoperfusion arises when white blood cells crowd the microvasculature and inhibit oxygen delivery through multiple mechanisms, including cytokine activation and high

metabolic activity. Leukostasis commonly presents with respiratory dysfunction or neurological deficits, and prompt treatment of the hyperleukocytosis is indicated.

Three approaches are used to achieve cytoreduction: induction chemotherapy, leukapheresis, and hydroxyurea. Induction chemotherapy is usually favored unless the patient has renal insufficiency, severe electrolyte abnormalities, or other factors that would postpone induction. Patients receiving induction chemotherapy are at high risk for developing tumor lysis syndrome, and prophylaxis against this syndrome is warranted. Leukapheresis is somewhat controversial, because it has not been shown to improve survival. It is typically used in patients who have symptomatic hyperleukocytosis and cannot undergo induction chemotherapy. Leukapheresis is available only at major medical centers and is not recommended for patients with acute promyelocytic leukemia, because the procedure may worsen the coagulopathy associated with this subtype of leukemia. Hydroxyurea is commonly used in patients who have asymptomatic hyperleukocytosis and cannot begin induction chemotherapy immediately.

In leukemic patients who present with tachypnea and respiratory distress without the presence of pulmonary infiltrates, leukostasis and pulmonary embolism should be considered. Pseudohypoxemia should be considered in patients with myeloproliferative disorders presenting with hyperleukocytosis or even thrombocytosis. This phenomenon occurs when oxygen consumption is increased by the markedly elevated white blood cells or thrombocytes in the arterial blood samples sent to the laboratory and reduces the PaO_2 content below the in vivo level. The greater the delay in processing the blood test, the lower the PaO_2 in the sample. Point-of-care testing often provides a more accurate blood gas picture.

Leptomeningeal Disease

Patients with leptomeningeal disease may present with a wide variety of neurological dysfunctions, including cranial neuropathies, myelopathies, or symptoms referable to cerebral hemispheric dysfunction. This is most commonly seen in hematological malignancies such as acute myelocytic leukemia and non-Hodgkin lymphoma. The most common solid tumors associated with leptomeningeal disease are lung and breast cancer and melanoma.

For diagnosis, imaging studies are typically performed prior to lumbar puncture.

An MRI of the brain and/or spine may help assess the extent of disease. Lumbar puncture with cytological findings of malignant cells is diagnostic of leptomeningeal disease, although if cytological findings are negative, abnormally high protein levels, low glucose, and elevated opening pressure would support the diagnosis in patients who are suspected to have leptomeningeal disease.

Given the typical presentation with an acute neurological deficit, these patients are treated as oncological emergencies; however, treatment of leptomeningeal disease is considered palliative. Palliative measures can include cranial irradiation, ventriculoperitoneal shunting for hydrocephalus, or intrathecal chemotherapy.

Acute Abdomen

Bowel Obstruction

Malignancies are the second most common cause of small bowel obstructions, and malignancy is the most common association in adults with intussusception. Bowel obstruction occurs most commonly in ovarian and colorectal carcinomas, although intraluminal tumors, such as lymphoma and carcinoid, can develop gradual progression of symptoms of bowel obstruction. Radiation therapy for intra-abdominal tumors can lead to the development of strictures and resulting bowel obstructive symptoms, especially in patients with prior abdominal surgery.

The presentation of a more proximal small bowel obstruction is usually characterized by persistent nausea and vomiting with crampy, paroxysmal abdominal pain but usually minimal distention. Colonic obstruction presents with more pronounced pain and distention and less commonly with nausea and vomiting. More severe and localized pain with these symptoms would suggest intestinal ischemia and/or strangulated obstruction.

Initially, abdominal imaging, including CT with contrast, is helpful in distinguishing between functional ileus and partial or complete obstruction and can help localize the cause.

Treatment should include attention to intravascular volume repletion and correction of electrolyte abnormalities. Nasogastric tubes are useful to decompress the stomach, and surgical consultation is recommended.

Typhlitis

Typhlitis, also known as neutropenic enterocolitis, describes a clinical syndrome of fever and right lower quadrant tenderness occurring in a neutropenic patient, usually after receiving cytotoxic chemotherapy. Although the cecum is most commonly affected, other areas of the distal small bowel or colon may be involved. This syndrome occurs more commonly in children, and patients usually have had neutropenia for more than 1 week. This syndrome has been ascribed to an overgrowth of *Clostridium* species, typically *Clostridium septicum*. Mucosal integrity is lost because of the cytotoxic chemotherapy, allowing the bowel wall to become infected. Patients with typhlitis usually present with fever and abdominal pain and may have rebound tenderness consistent with an acute abdomen. Bloody diarrhea is not uncommon, and some patients experience nausea and vomiting. The differential diagnosis includes appendicitis, pseudomembranous colitis, acute colonic pseudo-obstruction, ischemic colitis, and inflammatory or infectious colitis. CT and MRI are more diagnostically sensitive than plain images or ultrasonography. Treatment is conservative management, with supportive care until the neutropenia resolves. Patients should receive broad-spectrum antimicrobial agents, including coverage for enteral anaerobes. Most patients with typhlitis eventually improve, but the mortality rate is increased. Surgical intervention should be considered if gastrointestinal bleeding is persistent, if there is evidence of perforation, or if the clinical syndrome is one of progressive septic shock despite supportive care.

METABOLIC CRISES

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is caused by the rapid lysis of malignant cells, which releases toxic intracellular substances into the circulation. It occurs most often in patients with large tumor burdens that are highly responsive to chemotherapy or radiation, such as acute leukemia with hyperleukocytosis or high-grade lymphomas, although this syndrome can be seen with treatment of solid tumors.

The syndrome is typically characterized by a set of metabolic abnormalities, including acute hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. These derangements can occur individually or simultaneously.

The potential for life-threatening complications is high and is mostly related to cardiac arrhythmias from hyperkalemia or to further metabolic complications from renal failure. The metabolic derangements can evolve over a brief time interval, and close observation in an intensive care setting may be considered. Frequent laboratory testing is recommended during the acute phase of treatment in patients who are at high risk. The severity of the syndrome is predicted by extensive disease, particularly with bulky intra-abdominal tumors, elevated lactate dehydrogenase, preexisting renal insufficiency, and hyperleukocytosis.

Management of TLS is prescribed based on the specific metabolic disturbances and the stage they present. The Cairo-Bishop system is currently used for classification of TLS as a laboratory or clinical syndrome and for grading from 0 to V. Laboratory TLS occurs when 2 or more of the following are present: uric acid greater than 8 mg/dL or a 25% increase, potassium greater than 6 mEq/L or a 25% increase, phosphate greater than 4.5 mg/dL or a 25% increase, and calcium less than 7 mg/dL or a 25% decrease. Clinical TLS occurs when there is evidence of laboratory TLS plus 1 of the following: increased creatinine 1.5 times above the normal range, seizures, cardiac arrhythmias, or sudden death.

Once the syndrome develops, one of the most important initial interventions is to hydrate the patient to prevent renal dysfunction or failure. Following hydration, the maintenance of high-output diuresis (>2 mL/kg/h) with loop diuretics may be useful. Initial reduction of uric acid levels is accomplished with allopurinol, but several studies have demonstrated the superiority of rasburicase to control the metabolic disorder. However, rasburicase is contraindicated in patients with glucose 6-phosphate dehydrogenase deficiency because the hydrogen peroxide produced during uric acid breakdown leads to methemoglobinemia and to hemolytic anemia in the most severe cases. Renal replacement therapies are often considered early in the course of patients with TLS.

Hyperuricemia

As a result of hyperuricemia, patients develop precipitation of uric acid crystals in the renal tubules and acute renal failure. Aggressive IV hydration, urine alkalinization, and allopurinol are all useful treatments for hyperuricemia. Rasburicase (recombinant urate oxidase) can be useful, particularly in patients with leukemias or advanced lymphomas. Caution is recommended when allopurinol is used, because it requires dose reduction in renal insufficiency and can potentiate the effects of degradation of certain chemotherapeutic agents, such as 6-mercaptopurine, cyclophosphamide, and azathioprine. Vigorous

urinary alkalinization can lead to calcium phosphate precipitation in the urinary tubules and can worsen the neurological manifestations of hypocalcemia.

Hyperkalemia

Hyperkalemia should be anticipated in all patients at increased risk for TLS. Initially, potassium intake should be restricted and consideration may be given to enhancing potassium elimination with diuretics (if the patient is adequately hydrated). If the potassium level is greater than 7 mEq/L, elimination should be further enhanced by administration of oral sodium-potassium exchange resins, and consideration should be given to administration of dextrose and insulin, sodium bicarbonate, and β-agonists. Intravenous calcium should be considered in patients with hyperkalemia to protect against arrhythmias. Hemodialysis may become necessary to treat life-threatening hyperkalemia, particularly in patients with TLS complicated by acute renal failure.

Hypercalcemia of Malignancy

Hypercalcemia occurs in 20% to 30% of patients with cancer, most commonly in patients with lung cancer, breast cancer, or multiple myeloma. Patients typically present with nausea, vomiting, and altered mental status and can also exhibit constipation and renal failure. The altered mental status can progress to coma, and these patients are at increased risk for aspiration.

Treatment includes aggressive hydration with normal saline, followed by diuresis with loop diuretics. Thiazide diuretics should not be used, as these agents promote renal calcium reabsorption. These patients may have extreme intravascular volume depletion as a result of the hypercalcemia itself, which promotes renal diabetes insipidus, and as a result of nausea, vomiting, and altered mental status. Careful assessment should be made regarding adequate volume resuscitation prior to initiation of diuretic therapy. Intravenous bisphosphonates are effective, as they inhibit bone resorption by osteoclasts. Zoledronic acid and pamidronate are commonly used bisphosphonates. Other adjunctive treatments may include corticosteroids, calcitonin, plicamycin, gallium nitrate, and potentially dialysis. Hypophosphatemia is often coexistent with hypercalcemia and should be corrected due to the risk of rhabdomyolysis.

SYMPTOMATIC CYTOPENIAS

Febrile Neutropenia

Neutropenic fever is a true medical emergency, in that many cancer patients die of infectious complications arising in the setting of neutropenia. Fever may be the only indication of a life-threatening underlying infection. Algorithms have been developed to assist clinicians and have been modified by the best available clinical evidence, most recently by the Infectious Diseases Society of America, which developed a Fever and Neutropenia Guideline update in 2010.

Experts consider patients to be at high risk for neutropenic fever in the presence of expected prolonged neutropenia or profound neutropenia (absolute neutrophil count <100 cells/mm^3), hypotension, respiratory insufficiency, new-onset abdominal pain, or neurological changes. These patients should be admitted to a hospital for empirical IV therapy and close observation, as they are at very high risk to rapidly deteriorate. The clinician should order blood cultures, including cultures from indwelling venous catheters and from other sites of suspected infection, and chest radiography should be performed.

Initial empirical antibiotic treatment should include monotherapy with an antipseudomonal β-lactam agent, either cefepime or a carbapenem. Other antimicrobials are recommended if septic shock is present or antimicrobial resistance is suspected. Vancomycin can be added for specific clinical indications, such as suspected indwelling catheter–related bloodstream infection or skin or soft tissue infection. Vancomycin is often added as part of the regimen for patients in septic shock or with radiographic evidence of pneumonia. In patients with a history of vancomycin-resistant *Enterococcus*, linezolid or daptomycin should be considered. Antifungal agents should be considered for a patient who has persistent or recurrent fever beyond 4 to 7 days and whose overall duration of neutropenia is prolonged or if there are signs or symptoms suggestive of an invasive fungal infection.

Thrombocytopenia and Bleeding

Thrombocytopenia, a decline in platelet count, is almost always present in critically ill patients with hematological malignancies. Severe thrombocytopenia is a biomarker of bleeding and death in the critically ill cancer patient. In patients who have received chemotherapy, chemotherapy-induced thrombocytopenia is expected, and its severity depends on the specific cytotoxic agent used. The current therapy for thrombocytopenia remains allogeneic platelet transfusions when patients are actively bleeding or are at high risk for

bleeding. Determining when to transfuse is one of the main challenges for clinicians.

This risk of bleeding due to thrombocytopenia is modified according to the underlying type of cancer. In myelodysplastic syndrome and leukemias, increased risk of mortality due to thrombocytopenia-related bleeding has been demonstrated compared with other types of cancer.

DIRECT TREATMENT-RELATED EMERGENCIES

Extravasation of Chemotherapeutic Agents

Extravasation of chemotherapeutic agents may lead to local pain, erythema, induration, and even necrosis. Occasionally, a delay between the extravasation event and onset of symptoms occurs. This is caused by endocytolysis, in which a small amount of drug induces lysis of cells in a systematic way around the site. If large areas of skin break down, secondary infection may occur. The most common agents causing such issues include the vesicants, such as anthracyclines (doxorubicin, idarubicin), or vinca alkaloids (vincristine, vinblastine).

If extravasation occurs, the infusion should be discontinued and the line aspirated to remove residual drug. A table of antidotes should be consulted and the appropriate treatment initiated. Examples of antidotes include hyaluronidase for vinca alkaloids and paclitaxel, sodium thiosulfate for cisplatin, and dimethyl sulfoxide for mitomycin C and anthracyclines. Compression of the site is not typically recommended, because this can spread the extravasated drug further from the site, potentially causing more damage.

Hemorrhagic Cystitis

Hemorrhagic cystitis often occurs in cancer patients as a side effect of chemotherapy or pelvic irradiation or in association with infections, particularly the BK polyomavirus. This condition may not require critical care admission, but immediate attention often is necessary to avoid loss of organ function. Patients are at risk for symptomatic anemia, urinary obstruction with renal failure, significant pain, and infections.

A wide variety of cancer chemotherapeutic agents have been associated with hemorrhagic cystitis, the most common being cyclophosphamide and ifosfamide. Acrolein is a metabolite common to these drugs and is directly toxic to urothelial

cells. Drug dosages may be reduced or alternative chemotherapeutic agents administered. Mesna (2-mercaptoethane sulfonate) is often used to prevent hemorrhagic cystitis caused by ifosfamide, as it forms a nontoxic complex with acrolein.

Radiation therapy to the pelvic area may be complicated by hemorrhagic cystitis. Late or delayed damage caused by radiation can be irreversible and progressive, despite multiple modes of treatment.

Infectious causes of hemorrhagic cystitis are not uncommon in cancer patients. The BK polyomavirus, and to a lesser extent cytomegalovirus and several subtypes of adenovirus, are associated with hemorrhagic cystitis. The BK virus is often seen in bone marrow transplant patients. Bacterial infections, such as *Escherichia coli*, *Proteus*, and *Klebsiella*, and fungal infections with *Candida*, *Cryptococcus*, and *Aspergillus* must also be considered as causes of hemorrhagic cystitis. Parasitic organisms, such as *Schistosoma haematobium*, should be considered in patients at risk for such.

For patients with massive hematuria, the first step should be insertion of a large-bore urinary catheter with ports to allow continuous bladder irrigation. This will decompress the bladder, will flush out clots, and may slow or stop further hemorrhage. Cystoscopy may be attempted to allow fulguration of bleeding vessels. In centers with such capability, angiographic selective embolization may be an option. Surgical cystectomy may be considered if other therapies fail.

Specific Toxicity Syndromes

Ifosfamide Neurotoxicity

Ifosfamide, an alkylating agent, is often a component of chemotherapy regimens for treatment of gynecological and head and neck cancers, sarcomas, and lymphomas, as well as many pediatric malignancies. Encephalopathy is a severe, potentially fatal adverse effect of ifosfamide treatment, and patients with low serum albumin, renal insufficiency, or abdominopelvic tumors are at increased risk.

Patients usually present with confusion, either during or shortly after drug infusion. Approximately 30% of patients with this syndrome will develop hallucinations or psychosis, and some exhibit incontinence or muscle twitching. Rarely, patients develop nonconvulsive status epilepticus.

The diagnosis of ifosfamide neurotoxicity is supported by normal brain imaging in the setting of recent ifosfamide administration. Electroencephalogram findings are typically consistent with a metabolic encephalopathy.

Ifosfamide encephalopathy usually resolves completely within 1 to 3 days after administration is stopped. Methylene blue is an option in the treatment of this syndrome, particularly in patients with more severe toxicity. Intravenous albumin, particularly in patients with low serum albumin levels, may be useful.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a unique pattern of brain edema that occurs in the setting of neurotoxicity. In oncology, PRES has been associated with allogeneic bone marrow transplant and cancer chemotherapy, including cytarabine, cisplatin, gemcitabine, and bevacizumab.

The clinical presentation of PRES varies but often includes headache, visual changes, and altered mental status. Seizures may occur, and altered mental status may progress to coma. Hypertension is usually present and is moderate to severe. Thrombotic microangiopathy may also exist, supporting the diagnosis of thrombotic thrombocytopenic purpura.

Imaging with CT or MRI reveals focal regions of hemispheric edema that is usually symmetrical, more commonly seen in the parietal and occipital lobes. The frontal lobes, cerebellum, and inferior temporal–occipital junction may be affected.

The management of patients with PRES focuses on removing or discontinuing the presumptive cause, which usually includes stopping chemotherapy. Lowering blood pressure is crucial, with a recommended mean arterial pressure goal of 105 to 125 mm Hg and no greater than 25% reduction of the initial mean arterial pressure in the first hour. Recommended agents include nicardipine, labetalol, and nitroprusside continuous infusions. Careful attention to airway protection is necessary, because these patients may develop progressive neurological deterioration or seizure activity.

Retinoic Acid Syndrome

All-*trans* retinoic acid (ATRA) is a common component of treatment for patients with acute promyelocytic leukemia. Although ATRA is usually well tolerated, some patients develop a potentially life-threatening syndrome related to its

administration.

The retinoic acid syndrome is characterized by fever, leukocytosis, and respiratory distress, often accompanied by interstitial pulmonary infiltrates and pleural and pericardial effusions. Some patients develop acute renal failure or hypotension.

Establishing the diagnosis of retinoic acid syndrome is often challenging, because these patients are at increased risk for pulmonary infections and sepsis by the nature of their underlying disease. Patients receiving concurrent chemotherapy seem to have less risk of developing this syndrome, but it should be considered when patients receiving ATRA develop unexplained dyspnea, weight gain, or pulmonary infiltrate.

If this syndrome is suspected, ATRA should be discontinued, and corticosteroids, such as dexamethasone, should be initiated. A typical dexamethasone dose for this indication is 10 mg IV twice daily for at least 3 days.

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CHAPTER 33

Acute and Chronic Renal Failure and Management (Including Hemodialysis and Continuous Renal Replacement Therapies)

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Key words: acute kidney injury, renal replacement therapy

Acute kidney injury (AKI), formerly known as acute renal failure, is defined as a sudden decrease in kidney function resulting in the accumulation of creatinine, urea, and other nitrogenous waste products. This process is often accompanied by decreased urine output, salt and water retention, metabolic acidosis, hyperkalemia, and hyperphosphatemia. AKI is common in hospitalized patients and is associated with significant short- and long-term mortality, increased risk for the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD), and high healthcare costs.

EPIDEMIOLOGICAL CHARACTERISTICS

The reported incidence of AKI varies markedly depending on the definition of AKI used, the cause of AKI, and the patient population. Different studies have estimated the incidence of AKI to be 1% to 20% in hospitalized non-ICU patients and 20% to 67% in ICU patients. The most common cause of AKI in hospitalized patients is acute tubular necrosis (ATN) from ischemia, nephrotoxins, or sepsis. AKI has a poor prognosis, and mortality ranges from 10% to 80% depending on the patient population studied. Patients presenting with AKI and multiorgan failure have been reported to have mortality rates of over 50%. If renal replacement therapy (RRT) is required, the mortality rate can be as high as 80%.

DEFINITION AND STAGING

The major obstacle to AKI research has been the lack of a standardized definition in the literature, making comparisons between studies difficult. As a result, several consensus definitions of AKI have been sequentially developed in order to provide a uniform definition. These include the Risk, Injury, Failure, Loss, and ESRD (RIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO) classification systems. The RIFLE classification system, developed in 2004, stratifies AKI into 3 grades of increasing severity (Risk, Injury, and Failure) and 2 outcome measures (Loss and ESRD) (**Table 1**). The 3 graded stages (R, I, and F) are based on changes in serum creatinine (SCr), or estimated glomerular filtration rate (eGFR), and urine output. The diagnosis of AKI is made by fulfilling either the SCr or urine output criteria or both. RIFLE specifies that the change in SCr has to occur within 7 days. After emerging data demonstrated that even small changes in SCr were associated with adverse outcomes, AKIN modified RIFLE by adding an absolute change in SCr of 0.3 mg/dL or more as fulfilling criteria for AKI and by including a time constraint of 48 hours. The AKIN system also omitted the eGFR criteria, eliminated the Loss and ESRD outcome measures, and allocated patients who needed acute dialysis to stage 3. In 2012, the KDIGO system combined the strengths of AKIN and RIFLE by retaining two key criteria: (1) from AKIN, diagnosing AKI as an increase in SCr of 0.3 mg/dL within 48 hours, and (2) from RIFLE, allowing a time frame of 7 days for a 50% increase in SCr from baseline. The KDIGO definition is the preferred definition at this time. Multiple studies have validated the utility of these criteria in various populations, showing a correlation between more severe RIFLE and AKIN stages and worse clinical outcomes.

Table 1. RIFLE, AKIN, and KDIGO Criteria for AKI

RIFLE Class	SCr Criteria and GFR for RIFLE	UOP Criteria (for RIFLE, AKIN, KDIGO)	AKIN Stage	SCr Criteria for AKIN	KDIGO Stage	SCr Criteria for KDIGO
R	SCr increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/h for 6 h	1	SCr increase to 1.5- to 2-fold above baseline or by 0.3 mg/dL	1	SCr increase to 1.5- to 2-fold above baseline over 7 days or by 0.3 mg/dL within 48 h

I	SCr increase to 2-fold or GFR decrease >50% from baseline	<0.5 mL/kg/h for 12 h	2	SCr increase to 2- to 3-fold above baseline	2	SCr increase to 2- to 3-fold above baseline
F	SCr increase to 3-fold, GFR decrease >75% from baseline, or SCr ≥4 mg/dL (acute increase of at least 0.5 mg/dL)	<0.3 mg/kg/h for 24 h or anuria for 12 h	3	SCr increase >3-fold above baseline or ≥4 mg/dL with an acute rise of ≥0.5 mg/dL or patient receiving RRT	3	SCr increase >3-fold above baseline or ≥4 mg/dL with an acute rise of ≥0.5 mg/dL or patient receiving RRT
L	Complete loss of function for >4 weeks					
E	Complete loss of function for >3 months					

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; RIFLE, risk (R), injury (I), failure (F), loss (L), end-stage renal disease (E); KDIGO, Kidney Disease Improving Global Outcomes; RRT, renal replacement therapy; SCr, serum creatinine; UOP, urine output.

DIFFERENTIAL DIAGNOSIS

Although specific tests are not available for the diagnosis of AKI, a thorough history and complete physical examination should be undertaken to determine the following: rate of loss (acute vs prolonged decline in function), symptoms if present, concurrent diseases, and current and recent medications. **Table 2** lists several drugs known to cause or contribute to AKI. In addition, a review of blood chemistries (blood urea nitrogen, creatinine, serum electrolytes, albumin, and a complete blood count) and a complete evaluation of the urine (microscopy, sodium, creatinine, and osmolality) are essential. Acute oliguria may be associated with abdominal compartment syndrome. Abdominal compartment syndrome causes oliguria and AKI mainly by directly increasing renal outflow pressure and reducing renal perfusion. Measuring bladder pressure is essential in patients suspected of having abdominal compartment syndrome.

Table 2. Potential Causes of Drug-Induced Acute Kidney Injury

Causes	Examples
Prerenal	
Extracellular fluid volume depletion	Diuretics (excessive diuresis)

Decreased cardiac output	Negative inotropic drugs (especially in severe or decompensated heart failure)
Decreased systemic vascular resistance	Vasodilator antihypertensive medications
Increase renal vascular resistance	NSAIDs, cyclooxygenase 2 inhibitors, cyclosporine, tacrolimus, anesthetics
Decreased transcapillary pressure	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
Renal	
Acute tubular necrosis	Aminoglycosides, amphotericin B, radiocontrast agents, cisplatin, zoledronate, cocaine, antiretroviral agents (adefovir, cidofovir, tenofovir, and foscarnet)
Acute interstitial nephritis	Antimicrobial agents (penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, macrolides, tetracyclines, and rifampin), NSAIDs, cyclooxygenase 2 inhibitors, omeprazole, lansoprazole, phenytoin, valproic acid, cimetidine, ranitidine, diuretics, cocaine
Acute glomerulonephritis	NSAIDs, ampicillin, rifampin, lithium, penicillamine, hydralazine, gold, mercury, heroin
Postrenal	
Tubular precipitation	Acyclovir, methotrexate, sulfadiazine, foscarnet, indinavir, tenofovir, sulfonamides, triamterene, large-dose vitamin C (due to oxalate crystals), guaifenesin and ephedrine (nephrolithiasis)
Obstruction	
Bladder	Anticholinergic medications

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

Ultrasonography has limited utility for the majority of ICU patients given that prerenal azotemia and ATN represent the majority of cases. A reasonable initial approach may include volume expansion, placement of a bladder catheter, or, if a bladder catheter is already present, evaluation of the catheter for obstruction. However, ultrasonography is warranted in high-risk patients, in those presenting

from the community (where obstruction is more common), or after the initial evaluation has failed to reveal the potential cause of AKI. Although universal indications for renal biopsies are lacking, a biopsy may be necessary to assist in the diagnosis, determine the prognosis, and/or guide therapy. Renal biopsy is most useful in intrinsic renal failure not associated with ATN.

ETIOLOGICAL CONSIDERATIONS

AKI is generally divided into 3 categories: prerenal, intrinsic, and postrenal. Several renal indices can help differentiate between prerenal AKI (ie, prerenal azotemia) and ATN, as well as other causes of AKI (**Table 3**). Although useful, these variables can be influenced by several nonrenal factors. For example, SCr used to determine the ratio of blood urea nitrogen (BUN) to SCr (BUN:SCr) and to estimate glomerular filtration rate (GFR) can be influenced by both renal and nonrenal factors (**Table 4**). In addition, reaching steady-state SCr is often difficult given the variable rate of creatinine production, volume of distribution, and rate of elimination seen in critically ill patients. The fractional excretion of sodium (FENa) is often used, and a FENa less than 1% suggests a prerenal origin. FENa measures the ratio of sodium excreted (urine sodium × volume) to sodium filtered (serum sodium × GFR): FENa = ([UNa × SCr]/[SNa × UCr]) × 100, where U = urine, Na = sodium, S = serum, and Cr = creatinine. Although FENa is very useful when evaluating AKI, sodium excretion can be influenced by common ICU medications, most notably loop diuretics. Diuretics increase sodium excretion, making FENa less useful. In addition to FENa, a BUN:SCr ratio greater than 20:1 and a urine osmolality greater than 500 mOsm/kg are suggestive of prerenal injury.

Table 3. Common Renal Indices Found in Acute Kidney Injury

Type of Failure	BUN:SCr Ratio	U_{Na}, mEq/L	FENa (FEUrea)	Urine Osmolality, mOsm/kg H_2O	Urinalysis/Sediment (Typical Findings[a])
Prerenal	>20:1	<20	<1% (<35%)	>500	Specific gravity >1.020; normal, hyaline cast
Intrinsic					
Acute tubular necrosis	<20:1	>20 (usually >40)	>1%[b] (>35%)	<300	Specific gravity ~1.010; muddy-brown cast; epithelial cells, granular cast, WBCs, mild proteinuria

Acute interstitial nephritis	<20:1	Variable (usually >20)	<1% or >1% (>35%)	Variable (usually <300)	Hematuria, WBCs and possible cast, RBCs, epithelial cells, ± eosinophils, low to moderate proteinuria
Acute glomerulonephritis	>20:1	<20	<1% (<35%)	Variable (usually >500)	Dysmorphic RBC and RBC cast, ± eosinophils, moderate to severe proteinuria
Acute vascular syndrome	—	>20	Variable	Variable	Hematuria
Postrenal	>20:1	>20	Variable	<400 but variable	Variable (normal, hyaline cast, possible RBCs and/or WBCs, Bence-Jones proteinuria, crystals[c])

Abbreviations: BUN, blood urea nitrogen; FENa, fractional excretion of sodium; FEUrea, fractional excretion of urea; RBC, red blood cell; SCr, serum creatinine; U_{Na}, urine sodium concentration; WBC, white blood cell.

[a]Not seen in all cases.

[b]FENa can be low in radiocontrast nephropathy and pigment nephropathy; FENa is typically >3%.

[c]Calcium oxalate crystals with ethylene glycol ingestion; uric acid crystals in tumor lysis syndrome.

Table 4. Factors Influencing Measured Serum Creatinine and Urea

	Nonmedication Factors	**Medication Factors**
Serum creatinine	Muscle mass, age, race, sex, diet, neuromuscular disease	Trimethoprim, cimetidine
Urea	Liver impairment, diet, trauma or burns, internal blood loss	Corticosteroids, tetracycline

Prerenal Acute Kidney Injury

Prerenal AKI results from impaired renal blood flow and can be caused by several mechanisms. Decreased perfusion may occur from intravascular volume depletion, decreased effective circulation, or medications. Since the parenchyma is undamaged, the kidney responds by reabsorbing sodium in order to reabsorb water. This occurs when decreased perfusion is associated with intravascular volume depletion or when the effective circulating volume is decreased as

suggested by a FENa of less than 1%. If not corrected in a timely fashion, the lack of perfusion will result in ATN.

Drug-induced prerenal AKI typically results either from decreased blood flow to the kidney or from intraglomerular hemodynamic alternations. Extracellular volume depletion can be seen with excess diuretic use or when diuretics are used in patients with decreased effective circulation. Drugs that are associated with prolonged hypotension can lead to a further decrease in blood flow to the kidney. Drugs affecting the natural vasodilatation of the afferent arterioles or vasoconstriction of the efferent arterioles can result in prerenal AKI. Nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors decrease prostaglandins, which are partially responsible for vasodilating the afferent arteriole. Angiotensin-converting enzyme inhibitors and angiotensin receptor–blocking agents prevent efferent vasoconstriction by inhibiting the vasoconstrictor angiotensin II, therefore decreasing transcapillary pressure and the kidney's ability to maintain an adequate perfusion pressure. Calcineurin inhibitors (eg, cyclosporine and tacrolimus) can also cause prerenal AKI. The mechanism is not well understood but is believed to result from afferent vasoconstriction, although efferent vasoconstriction probably also occurs. In addition, acute interstitial nephritis has been associated with these agents.

Intrinsic Acute Kidney Injury

Intrinsic AKI occurs from injury to the renal tubules, glomerulus, vascular structures, or interstitium or from obstruction of the renal tubules. The FENa may be greater than 1%, less than 1%, or variable depending on the mechanism of the insult. For example, in ATN, the renal tubule is damaged and unable to reabsorb sodium, resulting in a FENa of greater than 1%. In the case of glomerulonephritis the renal tubules are intact, allowing sodium to be reabsorbed, and as a result the FENa is less than 1%.

Tubular Injury

ATN is common in critical illness and often results from ischemia associated with a prolonged prerenal insult or a direct nephrotoxin. Renal injury is usually reversible, but recovery may take days to weeks and may require short-term RRT. Irreversible damage is possible if ischemia is severe enough to cause cortical necrosis. Nephrotoxins most commonly associated with ATN include contrast agents, aminoglycosides, and amphotericin B, as well as several antiretroviral agents.

The urine sediment in ATN commonly demonstrates many tubular epithelial cells and coarse granular casts, often described as “muddy brown” casts. ATN is characterized by failure to maximally dilute or concentrate urine (isosthenuria). In prerenal azotemia, urine osmolality is usually greater than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg. However, exceptions exist.

Interstitial Injury

Acute interstitial nephritis (AIN) is characterized by inflammatory infiltrates and edema within the interstitium. The clinical presentation may include fever and rash with laboratory evidence of eosinophilia. However, this classic triad is seen in only 10% to 30% of patients with AIN. It is relatively uncommon, identified in 1% to 3% of all renal biopsies, unless associated with AKI. In this group, biopsy proven AIN accounts for 15% to 27% of cases.

Although the cause of AIN varies, drug-associated AIN is most common, representing more than 75% of cases. Other cases of AIN are caused by infections (5%-10%), some cases are idiopathic (5%-10%), and some cases are associated with systemic diseases (10%-15%). Recovery is usually complete but may take weeks to several months. Early steroid administration has been suggested to limit damage associated with drug-induced disease. AIN associated with the chronic use of calcineurin inhibitors is often irreversible.

Glomerular Injury

Acute glomerulonephritis refers to a specific set of renal diseases in which an immunological mechanism triggers inflammation and proliferation of glomerular tissue that can result in damage to the basement membrane, mesangium, or capillary endothelium. Urinary findings range from moderate to severe proteinuria (nephrotic category), dysmorphic erythrocytes, and erythrocyte casts (nephritic category). Rapidly progressive glomerulonephritis is frequently associated with systemic disorders such as lupus, hepatitis, vasculitis, and pulmonary renal syndromes. Typical complaints include fever, malaise, and arthralgia. Serological assays and kidney biopsy will identify most causes. Early recognition of this syndrome is extremely important because it can be fatal and result in irreversible kidney damage without prompt and aggressive treatment. Treatment with corticosteroids and cyclophosphamide has been shown to limit the disease.

Vascular Injury

Microvascular or macrovascular disease (major renal artery occlusion or severe abdominal aortic disease) can cause AKI. The classic microvascular diseases often present with microangiopathic hemolytic anemia and AKI occurring from glomerular capillary thrombosis, often with accompanying thrombocytopenia. Typical examples of these diseases are thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Atheroembolic disease is another important cause of irreversible AKI. Patients with atherosclerotic disease who undergo an invasive vascular procedure are at increased risk for AKI induced by atheroemboli.

Intratubular Obstruction

Intratubular obstruction from precipitation of either protein or crystals within the tubular lumen can cause AKI. Tubular obstruction can be caused by precipitated monoclonal light chains in multiple myeloma, uric acid from tumor lysis syndrome, calcium oxalate deposition from ethylene glycol, and drugs.

Postrenal Acute Kidney Injury

Postrenal AKI is uncommon in critically ill patients. If postrenal AKI occurs, the obstruction may be seen anywhere between the renal pelvis and the external urethral meatus. Obstruction may be intraluminal, in the wall, or extrinsic to the urinary tract. Obstruction can occur at the level of the bladder or urethra (lower tract obstruction) or at the level of the ureters or renal pelvis (upper tract obstruction). To cause AKI, upper tract obstruction must be bilateral or must affect a solitary functioning kidney. The obstruction blocks the flow of urine, leading to hydronephrosis with resultant damage to the renal parenchyma. If postrenal AKI is not treated promptly, the elevated tubular pressure can cause CKD.

If a urinary tract obstruction is suspected it can be ruled out with the placement of a bladder catheter. If a catheter is in place it should be evaluated for obstruction, and if obstruction is found it should be cleared or the catheter should be replaced. Ultrasonography is the gold standard test for diagnosis of upper tract obstruction. However, upper urinary tract obstruction may not be initially detected by ultrasonography in a patient who is volume depleted. Therefore, if upper urinary tract obstruction is suspected, ultrasonography should be repeated

once the patient is adequately fluid resuscitated.

BIOMARKERS FOR ACUTE KIDNEY INJURY

The serum concentration of creatinine is widely considered to be the most commonly used marker of renal function. SCr is a specific but generally insensitive biomarker that can change rapidly, resulting in non-steady-state levels that are misleading. In addition, an increase in SCr is generally seen several days after injury has occurred. For these and other reasons SCr is generally considered a poor marker of early AKI.

Ideally, a biomarker needs to detect injury early, provide for a differential diagnosis, and predict prognosis. Several biomarkers have been investigated in both adults and children with samples obtained from blood plasma, urine, or both. Some of the early and most studied biomarkers include neutrophil gelatinase-associated lipocalin, cystatin C, interleukin 18, and kidney injury molecule 1. More recently, 2 markers of cell cycle arrest (tissue inhibitor of metalloproteinases 2 and insulin-like growth factor binding protein 7) have been identified and together were shown to be superior to other markers of AKI in 700 critically ill patients. Based on this and an additional trial, on September 5, 2014, the US Food and Drug Administration approved marketing of NephroCheck (Astute Medical, San Diego, CA), a test that detects both insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases 2 in critically ill patients at risk of developing moderate to severe AKI within 12 hours of the test being performed.

COMMON CAUSES OF ACUTE KIDNEY INJURY IN CRITICAL ILLNESS

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a reversible, functional renal impairment that occurs in patients with portal hypertension due to liver cirrhosis, severe alcoholic hepatitis, or fulminant hepatic failure. HRS is characterized by a marked reduction in GFR in the absence of other causes of AKI. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Notably, tubular function is preserved with the absence of significant hematuria (<50 red blood cells per high-power field) and proteinuria (<500 mg/d) and lack of tubular histological changes. HRS is also diagnosed by the lack of

improvement in renal function after volume expansion with intravenous albumin (1 g/kg of body weight per day up to 100 g/d) for at least 2 days and withdrawal of diuretics.

HRS occurs in about 4% of patients with cirrhosis and ascites, with a cumulative probability of 18% at 1 year and 39% at 5 years. HRS occurs in approximately 25% to 30% of patients with acute liver disease. Two subtypes of HRS have been identified. Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of initial SCr to a level greater than 2.5 mg/dL or by 50% reduction in creatinine clearance to a level less than 20 mL/min in less than 2 weeks. Type 2 HRS is characterized as a moderate, steady renal failure with SCr greater than 1.5 mg/dL and refractory ascites. The onset of renal failure can be precipitated by an acute insult, such as spontaneous bacterial peritonitis or gastrointestinal bleeding. Without treatment, most patients with HRS die within weeks of the onset of the renal impairment. Patients with type 1 HRS have a median survival of 2 weeks, while patients with type 2 HRS have a median survival of 3 to 6 months.

Given the dismal prognosis of patients with type 1 HRS, aggressive therapy usually is indicated only for patients who are waiting for a liver transplant or undergoing evaluation to determine candidacy for transplant. General management includes withholding diuretics, limiting dietary sodium, restricting free water in hyponatremic patients, excluding other causes for AKI, and looking for precipitating factors (especially spontaneous bacterial peritonitis). Patients with type 2 HRS are typically less sick and can be managed as outpatients. Patients with type 1 HRS, however, require inpatient care with frequent monitoring of fluid intake, blood chemistry levels, and urine output. Beyond general management, therapeutic interventions include pharmacological treatment with vasoconstrictors and albumin, placement of a transjugular intrahepatic portosystemic shunt in select patients, RRT, and liver transplant. RRT is usually reserved for patients with severe AKI who are planned for liver transplant. Liver transplant is the only therapy that affects long-term mortality.

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or long-term dysfunction in one organ induces acute or long-term dysfunction of the other. As an example, worsening heart failure (HF) leads to reduced renal perfusion and, if severe enough, results in prerenal AKI. In contrast, patients with CKD have an increased risk of cardiovascular diseases.

CRS is characterized by the triad of concomitant decreased kidney function, therapy-resistant HF with congestion (ie, diuretic resistance), and worsening kidney function during HF therapy. The prevalence of renal insufficiency in patients admitted with HF is approximately 30% to 60%. Renal dysfunction is an independent risk factor for all-cause mortality in HF patients. Both elevated SCr on hospital admission and worsening creatinine during hospitalization predict poor outcomes. CRS has been classified into 5 types (**Table 5**). Types 1 and 3 describe acute changes in either the heart (type 1), leading to AKI, or the kidney (type 3), leading to cardiac dysfunction. Types 2 and 4 describe chronic changes in the heart and kidney. In type 2 CRS, chronic heart disease leads to CKD; in type 4 CRS, CKD leads to chronic heart disease. Secondary CRS (type 5) is preceded by a systemic event (eg, sepsis) that leads to simultaneous injury and/or dysfunction of both the heart (acute HF, acute coronary syndrome) and kidney (AKI, CKD). Management is challenging since no therapeutic agents have been shown to directly improve renal function in patients with CRS.

Table 5. Classification of Cardiorenal Syndrome

CRS Type	Primary Event	Definition/Secondary Event
Type 1	AHF or ACS or cardiogenic shock	Acute worsening of cardiac function leading to AKI
Type 2	Chronic heart disease	Chronic abnormalities in cardiac function leading to CKD
Type 3	AKI	Acute worsening of renal function leading to AHF, ACS, arrhythmias, shock
Type 4	CKD	CKD leading to cardiac injury (left ventricular remodeling and dysfunction, diastolic dysfunction, AHF, ACS)
Type 5	Systemic disease (eg, sepsis)	Simultaneous injury and/or dysfunction of heart and kidney due to acute or chronic disorders leading to AHF, ACS, AKI, CHD, CKD

Abbreviations: ACS, acute coronary syndrome; AHF, acute heart failure; AKI, acute kidney injury; CHD, congenital heart disease; CKD, chronic kidney disease; CRS, cardiorenal syndrome.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the massive and abrupt release of intracellular components into the blood following rapid lysis of malignant cells, leading to hyperuricemia, hyperkalemia, hyperphosphatemia,

hypocalcemia, and AKI. TLS is typically seen after initiation of cytotoxic therapy for hematological malignancies with large tumor burden or cell counts, as in acute lymphoblastic leukemia, Burkitt lymphoma, or acute myeloid leukemia, but may occur spontaneously as well. The incidence of AKI from TLS ranges from 7% to 45% in the adult population. The development of TLS-associated AKI is a strong predictor of death. Hyperuricemia causes AKI through precipitation of uric acid in the renal tubules, renal vasoconstriction, impaired renal autoregulation, and inflammation. Calcium phosphate deposition in the renal tubules from hyperphosphatemia can also cause AKI. In 2004, Cairo and Bishop presented a classification system for TLS based on laboratory findings or clinical condition (**Table 6**).

Table 6. Cairo-Bishop Definition of Laboratory and Clinical Tumor Lysis Syndrome (TLS)

Serum values in laboratory TLS[a] • Uric acid ≥8 mg/dL or 25% increase from baseline • Potassium ≥6 mEq/L or 25% increase from baseline • Phosphorus ≥6.5 mg/dL (children) or ≥4.5 mg/dL (adults) or 25% increase from baseline • Calcium ≤7 mg/dL or 25% decrease from baseline
Clinical TLS[b] • Serum creatinine ≥1.5 times the upper limit of normal for the age-adjusted normal range • Cardiac arrhythmia or sudden death • Seizure

[a]Laboratory TLS is defined as having 2 or more of the serum values listed within a time frame extending from 3 days before to 7 days after the initiation of chemotherapy.

[b]Clinical TLS includes the presence of one or more of the listed clinical states.

Principles for the management of patients at risk for or presenting with TLS include aggressive volume expansion to achieve a urine output of at least 80 to 100 mL/m^2/h, treatment of hyperkalemia and secondary hypocalcemia, and preventive therapy for hyperuricemia. Urinary alkalinization is no longer recommended since the high urine pH can cause an increase in calcium-phosphate crystal deposition. Allopurinol prophylaxis is recommended for patients at intermediate risk for TLS (eg, those with highly chemotherapy-sensitive solid tumors such as neuroblastoma, germ cell tumor, small-cell lung

cancer with bulky disease, or advanced stage disease), whereas rasburicase should be given to those patients at high risk (eg, patients with acute myeloid leukemia and a white blood cell count >100 × 10^9/L; adult T-cell leukemia or lymphoma; diffuse large B-cell, transformed, and mantle cell lymphomas with bulky disease and increased lactate dehydrogenase; stage III/IV childhood, diffuse large B-cell lymphoma with increased lactate dehydrogenase; Burkitt leukemia; or Burkitt lymphoma with elevated lactate dehydrogenase). Allopurinol acts as a competitive inhibitor of xanthine oxidase and decreases uric acid production. However, allopurinol cannot actively reduce preexisting high levels of serum uric acid, limiting its use to prevention. Rasburicase is effective in reducing high uric acid levels by directly catabolizing uric acid into allantoin, which is 5 to 10 times more soluble in urine than uric acid. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase or catalase deficiencies. Patients with established TLS require intensive nursing care with continuous cardiac monitoring and frequent measurement of electrolytes, creatinine, and uric acid. Management involves correcting electrolyte abnormalities, administering rasburicase (if not initially given and not contraindicated), administering intravenous fluids, and initiating RRT when indicated.

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is the third most common cause of AKI in the hospital. Although CIN is reversible in most cases, it is associated with increased morbidity and mortality. CIN is defined as an increase in SCr within 24 to 48 hours following contrast exposure (peaking up to 5 days afterward). The pathogenesis is not completely understood, but CIN is thought to be due to ATN from contrast-induced vasoconstriction, decreased renal blood flow, medullary hypoxia, oxidative stress, and direct tubular cytotoxicity. Renal failure tends to be nonoliguric, with FENa less than 1%. The urinary sediment may be bland or show classic findings of ATN. The risk of CIN increases with the severity of underlying renal dysfunction, especially among diabetic patients. The main risk factors for CIN are listed in **Table 7**. Preventive strategies for patients at high risk for CIN include using the lowest possible volume of contrast agent, using low or iso-osmolar contrast media, discontinuing nonsteroidal anti-inflammatory drugs and other nephrotoxins, and using either intravenous normal saline or isotonic sodium bicarbonate for volume expansion. Although the benefit of oral acetylcysteine in prevention of CIN remains unproven, many practitioners still administer it given its low risk and cost. There is no role for the use of

prophylactic hemodialysis or hemofiltration following contrast exposure. For established CIN, treatment is primarily supportive.

Table 7. Risk Factors for Contrast-Induced Nephropathy

Patient-related factors • Chronic kidney disease (glomerular filtration rate <60 mL/min/1.73m^2 body surface area) • Diabetes mellitus (type 1 or type 2) • Volume depletion • Nephrotoxic drug use (cyclosporine, nonsteroidal anti-inflammatory drugs, aminoglycosides) • Other comorbidities: anemia, hypoalbuminemia, multiple myeloma
Procedure-related factors • Higher volume of contrast • First-generation contrast agents • Emergent procedure • Length of procedure • Intra-arterial administration of contrast agent • Periprocedural hemodynamic instability

GENERAL MANAGEMENT OF ACUTE KIDNEY INJURY

In the majority of cases, AKI can be effectively treated by adequate volume replacement, treatment of the underlying medical condition, and avoidance of nephrotoxic medications. No specific pharmacological therapy is effective in established ATN. Potassium, magnesium, and phosphate should be restricted. Phosphate binders may be required to prevent severe hyperphosphatemia. Supplemental bicarbonate can be used to correct metabolic acidosis. Nutrition should be managed carefully to ensure adequate caloric and protein intake. In patients with severe AKI, initiation of RRT may be the only option.

RENAL REPLACEMENT THERAPY FOR ACUTE KIDNEY INJURY

RRT is used for supportive management of patients with severe AKI. There is a paucity of evidence to guide the optimal time to initiate RRT. At present, RRT is

initiated for the acute management of life-threatening complications of AKI, including severe hyperkalemia, metabolic acidosis, volume overload, overt uremic manifestations, and dialyzable intoxications. Although several meta-analyses of both randomized controlled trials and cohort studies have suggested that "early" initiation of RRT for AKI (based on a lower urea or creatinine level) is associated with better patient survival, these studies have significant design limitations and need to be confirmed with adequately powered randomized trials. Characteristically, clinicians take into account the overall clinical state of the patient, including degree of other organ system failures and likelihood of rapid renal recovery, and often start RRT prior to the development of overt AKI complications.

RRTs are classified by the predominant transport process used to remove solutes and toxins. All forms of RRT rely on the principle of allowing water and solute transport through a semipermeable membrane and then discarding the waste products. Ultrafiltration is the process by which water is transported by a transmembrane pressure gradient across a semipermeable membrane. Diffusion and convection are the two processes by which solutes are transported across the membrane. Diffusion occurs by movement of solutes from an area of higher solute concentration to an area of lower concentration across a semipermeable membrane. With extracorporeal dialytic techniques, the concentration gradient is maximized and maintained throughout the length of the membrane by running the dialysate (an electrolyte solution usually containing sodium, bicarbonate, chloride, magnesium, and calcium) countercurrent to the blood flow. Small-molecular-weight solutes, such as urea, are cleared efficiently by diffusion, but solutes of larger molecular weight are not. Convection occurs when the transmembrane pressure gradient drives water across a semipermeable membrane as in ultrafiltration but then "drags" with the water both small-molecular-weight solutes (urea, creatinine, potassium) and large-molecular-weight solutes (inulin, β-microglobulin, tumor necrosis factor, vitamin B_{12}). Membrane pore diameter limits the size of the large solutes that can pass.

The available RRT modalities use ultrafiltration for fluid removal and either diffusion, convection, or a combination of the latter two to achieve solute clearance. Options for RRT for AKI include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), "hybrid" therapies known as prolonged intermittent renal replacement therapy (PIRRT), and peritoneal dialysis (PD). **Table 8** summarizes several types of RRTs and their mechanism of solute removal. IHD, CRRT, and PIRRT are extracorporeal therapies and

require vascular access in the form of a large-bore, double-lumen central venous catheter; PD requires the placement of an intra-abdominal catheter for dialysis.

Table 8. Duration of Treatment and Characteristics of Solute Removal With Different Modalities of Renal Replacement Therapy

Technique	**Duration, h**[a]	Process of Solute Removal
Intermittent therapies		
Standard intermittent hemodialysis	3-4	Diffusion
Prolonged intermittent renal replacement therapy	6-12	Diffusion
Continuous therapies		
Peritoneal dialysis	Variable	Diffusion
Continuous venovenous hemofiltration	24	Convection
Continuous venovenous hemodialysis	24	Diffusion
Continuous venovenous hemodiafiltration	24	Diffusion and convection

[a]Duration may vary depending on patient needs and circuit performance.

Intermittent Hemodialysis

Typically, IHD is delivered in intermittent sessions of 3 to 5 hours, 3 to 6 times per week, using a blood flow rate of 300 to 500 mL/min and a dialysate flow rate of 500 to 800 mL/min. The duration and frequency of IHD sessions are determined by the patient's specific needs and degree of hemodynamic stability. In IHD, solute clearance occurs mainly by diffusion, whereas volume is removed by ultrafiltration. Advantages of IHD include rapid solute and volume removal. This results in rapid correction of electrolyte disturbances, such as hyperkalemia, and rapid removal of drugs or other substances in potentially fatal intoxications in a matter of hours. IHD is less likely to require anticoagulation compared with other types of RRT because of the faster blood flow rate and shorter duration of therapy. The main disadvantage of IHD is the risk of systemic hypotension caused by rapid electrolyte and fluid removal. Sodium modeling, cooling of the dialysate, increases in the dialysate calcium concentration, and intermittent ultrafiltration may be used to improve hemodynamic stability during IHD. Despite this, approximately 10% of AKI patients cannot be treated with IHD because of hemodynamic instability. Furthermore, rapid solute removal from the

intravascular space can cause cerebral edema and increased intracranial pressure, limiting this therapy in patients with head trauma or hepatic encephalopathy.

Peritoneal Dialysis

In PD, the peritoneum is used as a semipermeable membrane for diffusive removal of solutes. A dialysate solution is instilled into the peritoneal cavity through a catheter, where it dwells for a prescribed period of time allowing solutes to diffuse from blood in the capillaries into the dialysate. The saturated dialysate is then drained and discarded, and fresh dialysate is reintroduced. High concentrations of dextrose are used in the dialysate to create an osmotic gradient for ultrafiltration. Advantages of PD include technical simplicity, hemodynamic stability, and lack of need for anticoagulation or vascular access. Disadvantages include complications of PD catheter placement, risk of peritonitis, potential inability to provide sufficient solute clearance in hypercatabolic patients, unpredictable ultrafiltration, albumin loss across the peritoneal membrane, hyperglycemia, and potential respiratory compromise from increased abdominal pressure caused by instilled dialysate. PD is contraindicated in patients with recent abdominal surgery, abdominal drains, or ileus.

Continuous Renal Replacement Therapy

CRRT represents a variety of dialysis modalities developed specifically to manage critically ill patients with AKI who cannot tolerate IHD due to hemodynamic instability. CRRT uses diffusion, convection, or a combination of both for solute clearance and is performed up to 24 hours a day with blood flow rates of 100 to 300 mL/min. The most commonly applied modalities of CRRT are continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). In CVVH, solute clearance occurs by convection. No dialysate is used. The rate at which ultrafiltration occurs is the major determinant of convective clearance. Intravenous “replacement fluid” given through the extracorporeal device, is provided to replace the excess volume that is being removed and to replenish desired solutes. In CVVHD, solute removal occurs by diffusion. Unlike IHD, CVVHD entails a dialysate flow rate that is slower than the blood flow rate, allowing small solutes to equilibrate completely between the blood and dialysate. As a result, the dialysate flow rate approximates urea and creatinine clearance. Ultrafiltration is used for volume control. CVVHDF combines the convective solute removal of CVVH and the diffusive solute removal of CVVHD. With CVVHDF, as with CVVH, the high ultrafiltration

rates used to provide convective clearance require the administration of intravenous replacement fluids through the extracorporeal device. Despite increased clearance of middle-molecular-weight molecules with convective techniques, no study has shown that CVVH or CVVHDF improves patient survival compared with CVVHD. Since insufficient data are available to recommend one type of CRRT modality over another, the choice of CRRT modality should be based on clinician preference and expertise.

The advantages of CRRT include hemodynamic tolerance caused by slower ultrafiltration and solute removal. The gradual, continuous volume removal makes control of volume status easier and allows administration of medications and nutrition with less concern for volume overload. Because CRRT is a continuous modality, it entails less fluctuation of solute concentrations over time and allows better control of azotemia, electrolytes, and acid-base status. CRRT does not raise intracranial pressure, like IHD. The main disadvantages of CRRT include access and filter clotting, the consequent need for anticoagulation, increased costs, and demands on ICU nurse time compared with IHD.

Prolonged Intermittent Renal Replacement Therapy

Hybrid therapies are also known as PIRRT, sustained low-efficiency dialysis, and extended daily dialysis. These therapies use conventional hemodialysis machines with lower blood-pump speeds (ie, 200 mL/min) and dialysate flow rates (ie, 100-300 mL/min) to provide solute and fluid removal more slowly than IHD but more quickly than conventional CRRT. The duration of dialysis is extended to 8 to 16 hours daily. PIRRTs combine the advantages of both CRRT and IHD. PIRRTs allow for improved hemodynamic stability through gradual solute and volume removal as in CRRT. At the same time, PIRRTs are able to provide high solute clearances as in IHD and remove the need for expensive CRRT machines, costly customized solutions, and trained staff. Because PIRRTs can be performed intermittently based on the needs of the patient, they also avoid the interruption of therapy for various diagnostic and therapeutic procedures that may be required in such patients.

SELECTING RENAL REPLACEMENT THERAPY

Decisions for modality selection are hampered by lack of evidence for improved outcomes with specific modalities. Modality comparisons have failed to demonstrate any survival advantage for continuous versus intermittent therapy. In the absence of definitive data to support a particular modality, selection of

RRT modality should be based on the needs of the patient. Choice of RRT modality is also influenced by availability, expertise, resources, cost, and physician preference. Most clinicians choose IHD for AKI patients who are hemodynamically stable and CRRT or PIRRT for AKI patients who are hemodynamically unstable, are fluid overloaded, and/or have sepsis and multiorgan failure. IHD is also favored in patients who need rapid solute removal, such as patients with severe hyperkalemia or drug intoxications. CRRT is preferred in patients with cerebral edema since IHD may worsen neurological status by compromising cerebral perfusion pressure as a result of dialysis-associated hypotension or due to rapid intracellular fluid and solute shifts. Transitions in therapy are common and reflect the changing needs of patients during their hospital course. For instance, patients in the ICU may initially start on CRRT when they are hemodynamically unstable, transition to PIRRT when they improve, and leave the ICU receiving IHD.

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CHAPTER 34

Acute Acid-Base Disorders

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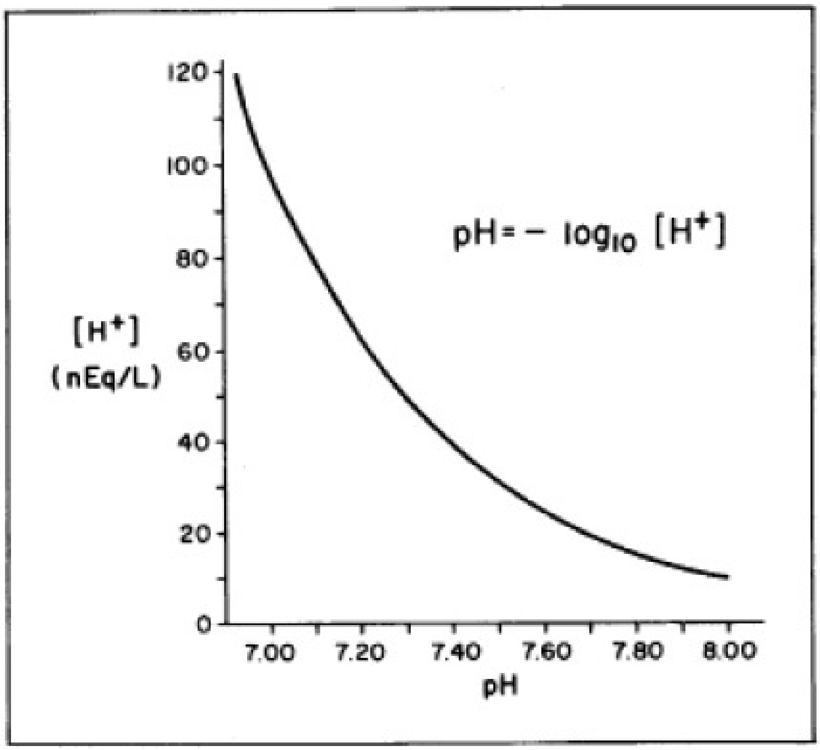
Key words: acute respiratory acidosis, acute respiratory alkalosis, metabolic alkalosis, metabolic acidosis, hyperchloremia

This chapter provides a basic understanding of acid-base physiology and offers a simple, practical approach to managing patients who manifest acute acid-base disorders. The reader is referred to more comprehensive reviews of chronic acid-base disorders.

NORMAL ACID-BASE PHYSIOLOGY

Acidity of body fluids is measured primarily in terms of hydrogen ion concentration ($[H^+]$) and is commonly expressed as hydrogen ion activity, or pH. The relation of $[H^+]$ to pH is straightforward and is depicted in **Figure 1**.

Figure 1. Relationship of hydrogen ion concentration $[H^+]$ to pH



For any given increase in $[H^+]$ a corresponding decrease in pH occurs, whereas any decline in $[H^+]$ is matched by an increase in pH. Hydrogen ions are abundant in the body and readily react with or dissociate from carbon, oxygen, nitrogen, and sulfur. Molecules that accept or donate hydrogen ions are called *buffers* and act to stabilize although not totally correct alterations in pH. Buffering is often defined by the following equation:

$$[HA] \leftrightarrow [A^-] + [H^+],$$

where [HA] is a weak acid and $[A^-]$ is the base. The extent to which a body buffer is able to stabilize pH depends on its ability to dissociate, which in turn is determined by its dissociation constant (pK). The closer the pK is to the normal pH of 7.40, the better the buffering capacity of that particular acid-base group. Of the biological fluids that function as buffers, the most important and prevalent system is the carbonic acid–bicarbonate pair. The relation of pH to this buffering system is conveyed by the Henderson-Hasselbalch equation:

$$\begin{aligned} pH &= pK + \log[HCO_3^-] \\ &= 6.1 + \log[HCO_3^-]\ [H_2CO_3]\ 0.03\ Pa_{CO_2}. \end{aligned}$$

Other nonbicarbonate buffers that aid in maintaining normal pH include plasma proteins such as albumin and hemoglobin, monobasic and dibasic phosphates,

and ammonium.

Applying the Henderson-Hasselbalch equation to a clinical situation is an arduous and clumsy task. A more practical and simpler approach emphasizing the interrelation of $[H^+]$, Pa_{CO_2}, and $[HCO_3^-]$ uses the Henderson equation:

$$[H^+] = \frac{24 \times Pa_{CO_2}}{[HCO_3^-]}$$

Henderson's equation is useful not only for a rapid calculation of $[H^+]$, Pa_{CO_2}, or $[HCO_3^-]$ once any 2 of the parameters are known but also for assessing the accuracy and internal consistency of the data presented. It is clear from this equation that the normal pH is 7.40, normal Pa_{CO_2} is 40 mm Hg, and normal $[HCO_3^-]$ is 24 mEq/L.

Although ranges in pH of 7.35 to 7.45 may be clinically irrelevant, for the sake of acid-base interpretation, a pH of 7.39 signifies acidemia and a pH of 7.41 alkalemia. (The terms *acidemia* and *alkalemia* apply to blood pH, whereas *alkalosis* and *acidosis* relate to tissue pH and clinical processes.) Note that between a pH of 7.2 and 7.5, a pH change of 0.01 units exists for approximately every 1 mEq/L change in $[H^+]$.

A primary metabolic acidosis is caused by a decrease in serum bicarbonate; likewise, a metabolic alkalosis occurs with an increase in serum bicarbonate. Primary respiratory acidosis and alkalosis occur with an increase or decrease in Pa_{CO_2}, respectively. The alteration in blood pH is therefore always determined by the Pa_{CO_2}:$[HCO_3^-]$ ratio. Maintaining a near-normal pH depends on appropriate compensatory mechanisms. A primary metabolic process induces a compensatory respiratory change: A primary respiratory process induces a compensatory metabolic change (**Table 1**). Compensation always moves the dependent (secondary) variable in the same direction as the independent (primary) variable to maintain the Pa_{CO_2}:$[HCO_3^-]$ ratio constant. Therefore, an easy rule for determining appropriate compensation is to note that the arrows always point in the same direction as seen in **Table 1**. When interpreting an acid-base disturbance, if the arrows are pointed in an opposite direction, a mixed acid-base disorder must exist (ie, 2 disorders occurring simultaneously). It is physiologically impossible to overcompensate to a normal pH of 7.40. The term *overcompensation* is incorrectly used for what is more accurately termed a *mixed disorder*. The appropriateness of the compensatory response is the essence of the

acid-base determination and is discussed in each section on primary acid-base disorders.

Table 1. Appropriate Compensatory Changes for Primary Acid-Base Disorder

Primary Disorders	Status	Compensation
Respiratory acidosis	↑ $Paco_2$	↑ $[HCO_3^-]$
Respiratory alkalosis	↓ $Paco_2$	↓ $[HCO_3^-]$
Metabolic acidosis	↓ $[HCO_3^-]$	↓ $Paco_2$
Metabolic alkalosis	↑ $[HCO_3^-]$	↑ $Paco_2$

ACUTE RESPIRATORY ACIDOSIS

Respiratory acidosis is almost always secondary to impairment in effective alveolar ventilation (VO_2). Rarely is an increase in carbon dioxide production ($\dot{V}CO_2$) the sole cause of a respiratory acidosis. However, in the setting of impaired or fixed minute ventilation, acute respiratory acidosis due to a marked increase in CO_2 can occur. The magnitude of pH change during acute respiratory acidosis therefore depends on both $\dot{V}CO_2$ and $PaCO_2$ elimination and can be defined by the following equation:

$$PaCO_2 = (K) \times \frac{\dot{V}CO_2}{Ve}$$

Note that when $\dot{V}CO_2$ is constant, any change in $PaCO_2$ is indirectly proportional to Ve. During the acute phase of a respiratory acidosis, nonbicarbonate buffering and renal adaptive mechanisms also play an important role in mitigating the decline in pH. The stimulus to increase Ve in response to an increase in $\dot{V}CO_2$ is primarily mediated by changes in the $[H^+]$ in the cerebrospinal fluid that bathes the chemoreceptor neurons of the central nervous system (CNS) located in the medulla. The responsiveness of the CNS appears to be mediated by the change in medullary $PaCO_2$ and, in turn, by the change in medullary $[H^+]$.

Following an acute increase in $PaCO_2$, a small increase in plasma bicarbonate is seen usually within 5 to 10 minutes and is primarily the result of the titration of intracellular noncarbonated buffers. Renal reabsorption of bicarbonate plays a

less important role during the acute phase of respiratory acidosis.

A primary acute respiratory acidosis is usually not associated with a plasma bicarbonate concentration greater than 32 mEq/L. A higher value almost certainly implies the association of secondary metabolic alkalosis. The appropriate increase in plasma bicarbonate for an acute respiratory acidosis can be determined by the following equation:

$$\Delta[HCO_3^-] = 0.1\ \Delta Pa_{CO_2} \pm 3.$$

Clinical Manifestations

The clinical manifestations of acute respiratory acidosis depend not only on the absolute magnitude of the Pa_{CO_2} but also on the rate of Pa_{CO_2} increase and the degree of associated hypoxemia. As previously mentioned, the CNS is sensitive to an acute increase in Pa_{CO_2}, with neurological manifestations ranging from anxiety and confusion to frank psychosis. Other neurological signs and symptoms include tremors, myoclonus, and asterixis. Hypercarbia causes cerebral vasodilatation that, when severe, can lead to increased intracranial pressure with associated headaches and papilledema. These changes are common with the acute and chronic stages of respiratory acidosis. Cardiovascular manifestations are also common in the setting of acute respiratory acidosis. The increases in heart rate and blood pressure, as well as the frequent occurrence of supraventricular and ventricular dysrhythmias, are thought to be secondary to the direct hypercarbic stimulation of the sympathetic nervous system. At the same time, an acute increase in Pa_{CO_2} can cause direct peripheral vasodilatation; however, the blood pressure is usually maintained or elevated because of the increase in cardiac output from sympathetic nervous system stimulation even though the patient appears warm and flushed.

Clinically significant acute respiratory acidosis is almost always associated with some degree of hypoxemia due to either pure alveolar hypoventilation with a lowered inspired oxygen or concomitant lung disease and impaired oxygen exchange. Many of the signs and symptoms associated with acute respiratory acidosis can be attenuated or exacerbated by an increase or a decrease in the Pa_{O_2}, respectively.

Causes

Disorders that can cause acute respiratory acidosis are listed in **Table 2.**

Table 2. Causes of Acute Respiratory Acidosis in the ICU

Upper airway obstruction	
	Posterior tongue displacement
	Foreign body
	Obstructed endotracheal tube
	Laryngospasm
	Aspiration
Lower airway obstruction	
	Severe bronchospasm
	Obstructive sleep apnea
Respiratory center depression	
	General anesthesia
	Sedative or narcotic overdose
	Intracranial surgery
Neuromuscular disorders	
	Prolonged depolarizing blockade (eg, pseudocholinesterase deficiency, phase II block in association with succinylcholine)
	Prolonged nondepolarizing blockade (eg, excess drug, hypothermia, aminoglycosides)
	Cervical cordotomy
	Myasthenia gravis crisis
	Guillain-Barré syndrome
Restrictive lung disorders	
	Hemothorax
	Pneumothorax
	Flail chest
	Acute lung injury
Miscellaneous disorders/increase $\dot{V}CO_2$	
	Malignant hyperthermia
	Circulatory arrest
	Maladjusted ventilator

Therapy

The early recognition and prompt alleviation of acute respiratory acidosis are essential to minimize the CNS and cardiovascular sequelae associated with severe hypercapnia and hypoxemia. During the postoperative period, simple maneuvers such as a jaw thrust or airway insertion may be sufficient to relieve an upper airway obstruction, but patients with more severe disorders such as prolonged neuromuscular blockade may require full mechanical ventilation with insertion of an endotracheal tube.

A number of pharmacological agents are important not only for minimizing but also for reversing acute respiratory acidosis. **Table 3** lists these particular drugs. The opioid antagonist naloxone is primarily used to treat narcotic overdose. Incremental dosing of naloxone seems prudent, as rapid reversal has been reported to precipitate acute pulmonary edema. This phenomenon is thought to be secondary to a massive catecholamine surge inducing a hydrostatic-mediated pulmonary edema and seems to be unique to the anesthesia recovery period. Because naloxone has a relatively short clinical effect, however, patients should be monitored closely for signs of recurrent hypoventilation. Anticholinesterase inhibitors reverse residual neuromuscular blockade and are useful for the treatment of myasthenia crises, which may require the systemic use of the anticholinesterase inhibitor pyridostigmine. Flumazenil, a competitive antagonist of the ***y***-aminobutyric acid receptor, is used to treat benzodiazepine overdose. Other drugs, such as inhalational bronchodilators and systemic corticosteroids, aid in treating severe bronchospasm, and diuretics such as furosemide help to alleviate severe pulmonary edema. Finally, in regard to alkali loading in patients with a pure, acute respiratory acidosis, the administration of sodium bicarbonate is contraindicated for 3 main reasons:

- Little if any change in acid-base equilibrium can be expected to occur when a normally functioning kidney excretes most of the bicarbonate fraction.
- In patients with impaired minute ventilation or impaired pulmonary perfusion, the amount of dissolved Pa_{CO_2} (260-280 mm Hg) in an ampule of sodium bicarbonate can significantly worsen both the venous and arterial acidosis.

- In patients with compromised cardiac and renal function, sodium bicarbonate administration can precipitate pulmonary edema, thereby worsening the respiratory acidosis and causing hypoxemia.

The appropriate use of alkali therapy is discussed in the section on metabolic acidosis.

Table 3. Pharmacological Therapy of Acute Respiratory

Naloxone
Anticholinesterase inhibitors
Flumazenil
Bronchodilators
Corticosteroids
Diuretics

ACUTE RESPIRATORY ALKALOSIS

Acute respiratory alkalosis occurs commonly in the critical care setting and is diagnosed by an arterial pH greater than 7.40 in the presence of Pa_{CO_2} less than 40 mm Hg. The terms *alveolar hyperventilation*, *primary hypocarbia*, and *hypocapnia* are all synonymous with *respiratory alkalosis.* The regulation of alveolar ventilation is governed by chemoreceptors located in the brainstem and in the carotid arteries and aortic arch. The chemoreceptors in the medulla are most sensitive to change in hydrogen ion concentration (as noted in the previous section on acute respiratory acidosis), whereas those in the carotid arteries and aortic arch are most sensitive to changes in oxygen delivery. Cortical input also plays a role in voluntary control of respiration. Finally, pathophysiological changes in the lung stimulate pulmonary chemoreceptors as well as “J” or stretch receptors and lead to hyperventilation. In response to the alkalemia induced by alveolar hyperventilation, secondary physiological responses attempt to mitigate the degree of pH change. Buffering takes place acutely in the extracellular space, with blood buffers such as hemoglobin and proteins playing a major role The degree of renal compensation for acute respiratory alkalosis is defined by the following equation:

$$0.1 \times \Delta Pa_{CO_2} \times (1\text{-}3).$$

Clinical Manifestations

Acute respiratory alkalosis induces changes in the CNS characterized by confusion and dizziness, although generalized seizures can occur. These changes relate to the hypocapnic effect on cerebral blood flow. Cerebrovascular resistance increases with the reduction in $Paco_2$, with marked impairment in cerebral blood flow at $Paco_2$ less than 25 mm Hg. In addition, an associated decrease in cerebral venous oxygen tension can lead to cerebral hypoxia, which may be the primary cause of seizures seen with acute respiratory alkalosis. Acute respiratory alkalosis is also associated with paresthesias in the extremities, chest pain, and circumoral numbness.

The cardiovascular changes most commonly described are tachycardia and a decline in stroke volume with minimal overall change in cardiac output or peripheral resistance. Cardiac dysrhythmias are common at extremes of pH (>7.60) and are often refractory to standard forms of treatment.

Metabolic abnormalities are also common during acute respiratory alkalosis. Intracellular shifts of sodium and potassium occur in response to the buffering effect of the hydrogen ion as it shifts to the extracellular space. Serum phosphate concentration is diminished because intracellular alkalosis activates the process of phosphorylation, thus depleting phosphate stores. This effect does not seem to be pronounced during metabolic alkalosis, appearing to be related solely to the intracellular hypocapnia. Finally, protein binding of calcium is increased during respiratory alkalosis and can cause or contribute to neurological changes, although a decrease in ionized calcium is unlikely to be the sole cause of seizures associated with acute respiratory alkalosis.

Causes

Table 4 lists the most common causes of acute respiratory alkalosis.

Table 4. Causes of Acute Respiratory Alkalosis in the ICU

Decreased oxygen delivery
Decreased oxygen content (anemia, hypoxemia)
Decreased cardiac output
Central nervous system stimulation
Voluntary stimulation
Anxiety
Pain
Fever

Stroke syndromes Infection (encephalitis, meningitis) Trauma Tumor Drugs (naloxone, methylxanthines, salicylates) Gram-negative sepsis
Hepatic failure
Pulmonary disease Asthma Pulmonary edema Pulmonary embolism Pneumonia Interstitial pneumonitis
Excessive mechanical ventilation

Therapy

The degree of alkalemia has been shown to correlate with high mortality in critically ill patients when the Pa_{CO_2} is less than 15 mm Hg; therefore, marked alkalemia needs to be treated aggressively. Unlike the case with acute respiratory acidosis, however, no pharmacological armamentarium is available to treat acute respiratory alkalosis. Therapy therefore is directed solely to the underlying cause. Severe anxiety can be treated by the patient rebreathing from a paper bag or by using anxiolytic agents such as benzodiazepines. Analgesic therapy for the patient in pain, oxygen therapy for the hypoxemic patient, and readjustment of mechanical overventilation are obvious ways of treating these particular causes of acute respiratory alkalosis.

METABOLIC ALKALOSIS

A metabolic alkalosis exists when plasma bicarbonate is greater than 24 mEq/L with an arterial pH of 7.40. When this form of alkalosis develops, it is primarily due to loss of titratable acid from either the gastrointestinal tract or the kidney or from the net addition of exogenous bicarbonate. The extrarenal buffering of metabolic alkalosis occurs primarily via the extracellular release of hydrogen ion from plasma proteins as well as by intracellular sodium-hydrogen and potassium-hydrogen exchange. Respiratory compensation occurs as the result of inhibition of the medullary chemoreceptors, leading to alveolar hypoventilation. The degree of compensation is based on the following:

$$\Delta[HCO_3^-] \times (0.8) = \Delta Pa_{CO_2}.$$

Because alveolar hypoventilation can be associated with low inspired oxygen concentration, the maximum pulmonary compensatory response to severe metabolic alkalosis is limited by hypoxemia. Oxygen delivery can be further impaired by the shift in the oxyhemoglobin dissociation curve to the left (Bohr effect), thus diminishing oxygen availability at the tissue level.

Metabolic alkaloses can be classified as either chloride responsive or chloride resistant and are discussed in more detail subsequently. For most critically ill patients, however, metabolic alkalosis is ordinarily either chloride responsive or due to an acute alkali load.

Clinical Manifestations

CNS changes can occur with severe metabolic alkalosis. Confusion, lethargy, and stupor have been attributed to the severity of pH increase. Refractory cardiac dysrhythmias, as mentioned in the previous section, also can occur. Metabolic changes associated with metabolic alkalosis include low ionized calcium due to increased protein binding at alkalemic pH levels as well as hypokalemia due to renal losses of potassium when hypovolemia stimulates the release of aldosterone in patients with chloride-responsive metabolic alkalosis.

Causes

The causes of metabolic alkalosis that are of concern are listed in **Table 5**.

Table 5. Causes of Metabolic Alkalosis in the ICU

Acute alkali administration
Gastric fluid losses
Postdiuretic therapy
Posthypercapnic states
Massive transfusions
Hyperaldosteronism
Cushing's syndrome
Nonresorbable anions

Therapy

The major goal of therapy for patients with metabolic alkalosis is to minimize the increase in pH, treating levels of pH 7.55 or more to prevent the cardiovascular and neurological sequelae. Prevention of metabolic alkalosis can be accomplished by minimizing excessive use of exogenous alkali or diuretics. Using histamine-2 blocking agents may be beneficial in reducing gastric hydrogen ion secretion, thereby minimizing acid loss in patients undergoing nasogastric suction. The major treatment modality for patients with chloride-responsive metabolic alkalosis is the infusion of sodium chloride. Normal saline offers more chloride per liter than does lactated Ringer's solution (154 vs 104-109 mEq/L, respectively) and is therefore the agent of choice in the nonedematous, hypovolemic patient. Lactated Ringer's solution may be contraindicated owing to the conversion of lactate to bicarbonate. For patients with edema (eg, congestive heart failure, cirrhosis, nephrosis), chloride is best administered as potassium chloride to avoid the potential for further volume overloading with normal saline. With severe metabolic alkalosis, dilute hydrochloric acid can be used by infusing 0.10 to 0.15 N hydrochloric acid solution slowly through a central IV catheter, titrating the therapy to lower the pH to less than 7.60. Acetazolamide is also a useful agent, especially in patients with posthypercapnic or edematous metabolic alkalosis. By causing carbonic anhydrase inhibition, acetazolamide creates bicarbonate diuresis, thereby lowering systemic pH. Replacement of renal potassium losses should be anticipated and treated accordingly.

METABOLIC ACIDOSIS

Metabolic acidosis is a primary disorder characterized by a reduction in the plasma bicarbonate level, which results in a lowering of the pH. Metabolic acidosis results from either a net addition of acid or a net loss of bicarbonate from the extracellular compartment. Rapid dilution of the extracellular space by bicarbonate-free solution such as isotonic saline also lowers plasma bicarbonate and yields a metabolic acidosis. The decrease in plasma bicarbonate is initially buffered by intracellular proteins, phosphates, and hemoglobin. Respiratory compensation occurs when the acidic pH stimulates the medullary chemoreceptors. This alveolar hyperventilation often takes 12 to 24 hours to reach a maximal effect. The degree of hyperventilation depends on the degree of metabolic acidosis. The relation of respiratory compensation to the decrease in plasma bicarbonate is defined by the following equation:

$$\Delta Paco_2 = \Delta[HCO_3^-] \times (1.2).$$

Therefore, a patient with a pH of 7.30 and a serum bicarbonate level of 16 mEq/L would be expected to hyperventilate to a $Paco_2$ of 30 to 31 mm Hg. If such a patient were noted to have a $Paco_2$ of 38 mm Hg, a secondary respiratory acidosis would be present. The astute clinician would recognize this mixed acid-base disturbance as a sign of potential respiratory muscle fatigue and institute early ventilator support rather than attempt to treat the metabolic acidosis with an infusion of sodium bicarbonate.

A metabolic acidosis can be characterized based on the net gain of acid or the net loss of bicarbonate by using the anion gap. The anion gap is based on the physiological concept of electroneutrality. Simply stated, the cations in the extracellular space precisely balance the anions. The major extracellular fluid cation is sodium (potassium primarily resides in the intracellular fluid space). Unmeasured cations (ie, those not routinely measured, such as sulfates and phosphates) constitute the remainder of the positively charged ions. The major anions include chloride and bicarbonate as well as the unmeasured anions. Therefore, unmeasured cations plus sodium should equal unmeasured anions plus chloride and bicarbonate. The anion gap formula is obtained by rearranging this equation as follows:

$$\text{Unmeasured Anions} - \text{Unmeasured Cations}$$
$$= Na^+ - (Cl^- + HCO_3^-).$$

The difference between unmeasured cations and unmeasured anions represents the anion gap. Any process that elevates the unmeasured anions thereby increases the anion gap. The relation between the anion gap and metabolic acidosis is based on the fact that additional unmeasured anions are organic acids. Therefore, an anion gap metabolic acidosis signifies the net addition of acid, and a non–anion gap metabolic acidosis signifies the net loss of bicarbonate.

Clinical Manifestations

The clinical features of metabolic acidosis are often related to the underlying disorders. However, direct effects on specific organ systems do occur, related primarily to the change in pH. Pulmonary manifestations include rapid and deep respiration, so-called Kussmaul respiration, and are most apparent when the pH is less than 7.20. An increase in pulmonary vascular resistance can also occur, contributing to the severity of pulmonary hypertension and/or right ventricular

failure. The degree of myocardial dysfunction associated with metabolic acidosis also depends on the level of the pH. When pH values are less than 7.20, myocardial contractility may be greatly diminished. At less severe changes in pH, cardiac output may be increased, as metabolic acidosis stimulates the release of catecholamines, thereby providing endogenous inotropy during the period of acidosis. Clinical and experimental studies show that a metabolic acidosis lowers the ventricular fibrillation threshold, predisposing the patient to life-threatening dysrhythmias. A decrease in vascular resistance also occurs with a metabolic acidosis, although it can be counterbalanced by the endogenous release of catecholamines. Metabolic acidosis causes a shift in the oxyhemoglobin dissociation curve to the right, thereby promoting the release of oxygen at the tissue level. Chronic metabolic acidosis causes a decrease in red blood cell 2,3-diphosphoglyceric acid, thereby shifting the oxyhemoglobin dissociation curve back to the left, conceivably adding to tissue hypoxia in certain hypoperfusion states. Gastrointestinal function is thought to be diminished during periods of metabolic acidosis as manifested by delayed gastric emptying.

Causes

Table 6 lists the causes of metabolic acidosis based on the anion gap calculation.

Table 6. Causes of Metabolic Acidosis in the ICU

Non–anion gap
Diarrhea
Pancreatic drainage
Carbonic anhydrase inhibitors
Biliary drainage
Urinary diversion (obstructed ileal loop conduit)
Hyperchloremic acidosis
Renal tubular acidosis
Adrenal insufficiency
Anion gap
Lactic acidosis
Ketoacidosis (diabetes, starvation, alcoholism)
Uremia
Acute toxin ingestion (methyl alcohol, ethylene glycol, paraldehyde, salicylate)

Therapy

Treatment of the underlying disorder is paramount to correction of a metabolic acidosis. To properly assess this acid-base disturbance, a clinician must

determine the presence or absence of an anion gap and establish a differential diagnosis based on this calculation.

Therapy for a non–anion gap metabolic acidosis consists of replacing IV volume losses with a low-chloride, bicarbonate-containing solution. Gastrointestinal losses of bicarbonate due to severe diarrhea or pancreatic or biliary drainage can be accomplished by adding sodium bicarbonate to 0.45% saline (adding 2 ampules of sodium bicarbonate to 1 L of 0.045% saline creates a solution with a high bicarbonate, low chloride content and a sodium content slightly greater than that of 0.9% saline). A hyperchloremic, non–anion gap metabolic acidosis from excessively high-chloride-containing IV solutions can be treated using hypotonic saline solutions when the patient is normovolemic or with a similar bicarbonate-containing solution as mentioned previously when the patient is hypovolemic. The diagnosis of hyperchloremia can be ascertained by merely dividing the serum sodium level by the serum chloride level. A ratio of less than 1.36:1 signifies hyperchloremia.

Although the treatment of certain anion gap metabolic acidoses is well established, the adjunctive therapy for other organic acidoses appears to be more controversial. This controversy centers primarily on the administration of sodium bicarbonate for the treatment of lactic acidosis. Based on experimental models, recommendations have been made to limit the use of sodium bicarbonate as a buffering agent for lactic acidosis, citing its minimal effect on correcting systemic pH and its potential for exacerbating acidemia.

Arguments against the use of sodium bicarbonate include the following:

- Because of sodium bicarbonate's high sodium content and high osmolality (2,000 mOsm/L), excessive administration can cause severe hypernatremia and hyperosmolality, and therapy can predispose patients to seizures or other neurological sequelae. Pulmonary and cerebral edema can be precipitated by excessive administration primarily in patients with poor myocardial, renal, or cerebral function.

- A severe alkalemia can occur owing to excessive bicarbonate administration in the setting of excessive mechanical ventilation. It can lead to a pH high enough to precipitate dysrhythmias or generalized convulsions.

- Sodium bicarbonate administration can result in an increase in $\dot{V}CO_2$ not

only because of the titration of bicarbonate by nonbicarbonate buffers to $Paco_2$ but also because of the release of the dissolved fraction of $Paco_2$ in an ampule of sodium bicarbonate (260-280 mm Hg). This situation can worsen the pH by adding a respiratory component to the systemic acidosis. A decrease in arterial pH occurs when Ve is impaired, and a venous acidosis may ensue when impairment to pulmonary blood flow leads to a failure to deliver $Paco_2$ to the lungs for elimination. The scenario is best exemplified during cardiopulmonary arrest, as discussed further subsequently.

- Lactic acid production can increase due to the effect of bicarbonate in enhancing the transformation of glucose and amino acids to lactic acid, thereby worsening the metabolic acidosis.
- Experimental studies fail to show improved survival when bicarbonate is used to treat lactic acidosis.

Arguments for the continued use of sodium bicarbonate include the following:

- Careful titration of sodium bicarbonate prevents severe hyperosmolality and pulmonary edema.
- Titrating sodium bicarbonate to achieve a serum level of 12 to 15 mEq/L should avoid the complication of severe alkalemia. Based on Henderson's equation, an increase in plasma bicarbonate from 6 mEq/L to 12 mEq/L in a patient with a $Paco_2$ of 20 mm Hg and pH 7.10 increases the pH to 7.30 despite a potential increase in the $Paco_2$ to 25 to 27 mm Hg. An appropriate dose of sodium bicarbonate is best determined by calculating the desired increment of change in plasma bicarbonate and then multiplying this change by the patient's weight in kilograms and by the volume of distribution of plasma bicarbonate. The volume of distribution depends on the pH: A pH of 7.00 yields a volume of distribution of bicarbonate at 80% of total body weight, whereas a pH of 7.20 to 7.40 yields a volume of distribution ranging from ~50% to 40%, respectively. Therefore, at a pH of 7.10, a 70-kg patient requires ~210 mEq of bicarbonate to raise the plasma bicarbonate from 6 mEq/L to 12 mEq/L, as noted in the following equation:

$$70 \text{ kg} \times 0.50 \text{ L/kg} \times 6 \text{ mEq/L} = 210 \text{ mEq}.$$

This replacement should be done slowly, with half the dose given over 8 to 12 hours and the remainder over the next 12 to 24 hours.

- The increase in $\dot{V}CO_2$ that occurs during sodium bicarbonate administration is of little consequence in a patient who is able to maintain Ve. However, when Ve is impaired or pulmonary blood flow is diminished, this issue may pose more of a problem when severe hypoperfusion or cardiopulmonary arrest is present. In such states, $PaCO_2$ elimination is impaired not only at the pulmonary level but also at the tissue level. That small proportion of pulmonary blood flow that does deliver $PaCO_2$ to the lungs can be effectively eliminated provided ventilation is effective. $PaCO_2$, therefore, may be normal. However, at the tissue level, continued lactic acidosis and tissue hypercarbia may yield a "paradoxical" or mixed venous acidosis that persists until adequate pulmonary blood flow can improve delivery of $PaCO_2$ to the lungs. This mixed venous acidosis represents a tissue or intracellular acidosis that can augment myocardial depression in the setting of electromechanical dissociation. Intravenous infusions of sodium bicarbonate in the setting of poor pulmonary blood flow therefore can worsen the mixed venous acidosis by providing an additional $PaCO_2$ load.

- Provided Ve is maintained, the lactic acid that may be generated with the use of sodium bicarbonate does not appear to be of major consequence.

- Finally, although a few experimental studies suggest improved survival when lactic acidosis is treated with bicarbonate, fewer clinical studies support this contention. At a pH less than 7.20, myocardial performance of a normal heart is usually not impaired because of an increase in sympathetic stimulation. However, at pH less than 7.10, severe hemodynamic compromise can occur; therefore, the careful titration of bicarbonate can improve cardiovascular responsiveness while other measures are instituted to correct the cause of the acidosis. In the setting of hypoperfusion and shock, the source of lactic acid is intracellular and, as such, the use of IV bicarbonate (ie, an extracellular approach to therapy) will not readily correct this problem. Indeed, with the production of acid often exceeding hundreds of milliequivalents per hour, use of sodium bicarbonate will rarely be able to buffer what is often a profound anaerobic state.

Other nonbicarbonate buffers have been used with some success to treat lactic acidosis. THAM (tromethamine, or *tris* buffer) is a potent amine buffer that combines with carbonic acid and increases the amount of available bicarbonate. Dichloroacetate reduces lactic acid by stimulating the enzyme pyruvate dehydrogenase, thereby catalyzing the oxidation of lactate to pyruvate. Although

these agents are well described, they are rarely used clinically. Finally, fomepizole (4-methylpyrazole) is a competitive inhibitor of alcohol dehydrogenase that prevents the formation of metabolites of methanol and ethylene glycol and is often used to treat these maladies.

ALTERNATIVE METHODS OF BLOOD GAS ANALYSIS

Standard Base Deficit

In 1958, Astrup and Siggaard-Andersen introduced *base deficit* as an improved method of measuring the metabolic component in blood gas analysis. This approach uses 3 variables to ascertain acid-base status: pH, $Paco_2$, and base excess (BE). Base excess is the amount of acid or alkali that must be added to blood that has been exposed in vitro to a $Paco_2$ of 40 mm Hg to achieve a pH of 7.40. When the pH is higher than 7.40, acid is required to return the pH to a baseline normal, and this is termed *positive BE* (or simply *BE*). When the pH is lower than 7.40, alkali is needed to return the pH to baseline and this is termed *negative BE* or *base deficit*. Under normal physiological conditions, BE ranges from –2 to +2 mEq/L. When studied in the laboratory, a $Paco_2$-induced increase in plasma bicarbonate concentration is matched by a decrease in the anionic charge of nonbicarbonate buffers, such as hemoglobin, to an equal degree. Base excess remains constant. The same is true for induced decreases in $Paco_2$. However, with episodes of hypoventilation or hyperventilation, thus altering $Paco_2$ in vivo, BE does not remain constant. This is due to a bicarbonate concentration gradient that develops between the plasma and the interstitial compartment. With hyperventilation, bicarbonate moves from the interstitial fluid into the plasma, which results in a positive BE. The opposite is true with hypoventilation. Bicarbonate moves from the plasma into the interstitial compartment resulting in a base deficit.

To more closely represent the behavior of human beings, standard base excess (SBE) was introduced, which is the BE calculated for a blood sample with the hemoglobin value of 5 g/dL. The reasoning behind this is that in the whole body, hemoglobin buffers the plasma as well as the larger volume of extracellular fluid, which can be compared to anemic blood. Thus, many blood gas analyzers calculate SBE from pH, $Paco_2$, and hemoglobin using the following equation:

$$SBE = 0.9287 \times [HCO_3^- \, 24.4 + (pH - 7.4)].$$

The SBE approach allows for 4 acid-base disorders. Metabolic disturbances have a primary change in BE, and the main change with respiratory disturbances is in the $Paco_2$. Calculating the anion gap will offer further assessment of the acid-base derangement. Although this method is commonly used and relatively easy to understand, it does not identify the source of the acid-base disorder and fails to recognize mixed or chronic acid-base disorders. Also, accurate calculation of the SBE and anion gap requires normal values of albumin and body water. The utility of SBE for evaluating critically ill patients has often been questioned.

Stewart Equation

In the early 1980s, Peter Stewart introduced yet another method of analyzing blood gases. He proposed that 3 variables determine the hydrogen ion concentration and therefore the pH: the strong ion difference (SID), the total weak acid concentration (A_{tot}), and $Paco_2$. The SID is the difference between fully dissociated anions and cations. It is mathematically represented with the equation $(Na^+ + Mg^{2+} + Ca^{2+} + K^+) – (Cl^– + A^–)$ and ranges from 40 to 44 mEq/L. Given their enormity, Na^+ and $Cl^–$ constitute the majority of this value. The A_{tot} value is mainly based on albumin and can be further described as A_{tot} = 2.43 × (total protein g/dL). In this approach, a bicarbonate value is noncontributory and only bridges the difference between strong anions and strong cations.

When this method is used in clinical practice, pH and $Paco_2$ must be measured and the apparent and effective SID and A_{tot} calculated. To simplify the calculation of the apparent strong ion difference (SIDa), Na^+ concentration is added to the K^+ concentration and $Cl^–$ concentration is subtracted from this sum. The effective strong ion difference (SIDc) is calculated from the following equation: SIDe = $[HCO_3^–] + [Alb^–] + [Pi^–]$, where [Alb] represents albumin (g/L) × [(0.123 × pH) – 0.631] and $[Pi^–]$ is inorganic phosphate (mmol/L) × [(0.309 × pH) – 0.469]. The difference between the SIDa and the SIDe is the strong ion gap (SIG), which enumerates the unmeasured strong anions. It is suggested to be more precise than the anion gap in measuring unmeasured anions.

The Stewart method allows for 6 acid-base disorders based on changes in SID, A_{tot}, and $Paco_2$. A low SIDe indicates a metabolic acidosis and can be associated with a high SIG, as in diabetic ketoacidosis, or with a normal SIG (zero), as in diarrhea. A high SIDe is consistent with metabolic alkalosis. Alternatively, a

high A_{tot} indicates a metabolic acidosis (hyperalbuminemic acidosis) and a low A_{tot} indicates a metabolic alkalosis (hypoalbuminemic alkalosis). Increases or decreases in $Pa{CO_2}$ represent a respiratory acidosis or alkalosis, respectively.

It has been argued that the SIG, with its complex variables and calculations, better predicts mortality in the critically ill population. Unfortunately, a paucity of studies support a diagnostic benefit with the use of this method. Not only is the Stewart method labor intensive, requiring the use of computers, additional laboratory measurements, and solving for both the SIDa and SIDe, it is also puzzling in that the SIDe requires $[HCO_3^-]$ despite statements claiming that it is an irrelevant anion. Also the 6 acid-base disorders that this approach discerns can be achieved multiple ways, rather than via one approach as in the traditional method. For example, metabolic acidosis can be associated with a normal or low SIDa, a normal or high SIG, or high A_{tot}. Last, albumin has a major contribution in determining the SIDe, even though albumin has no impact on $Pa{CO_2}$ or pH and has no relevance in clinical acid-base disorders.

KEY POINTS FOR ASSESSING AN ACUTE ACID-BASE DISORDER

Successful interpretation of acid-base data requires a systematic approach to each disorder **(Table 7)**. With such an approach, simple and complex abnormalities are detected, differential diagnoses are established, and early and appropriate therapeutic intervention is initiated. The following steps are offered as guidelines and apply to clinical evaluation of all acid-base disorders.

Table 7. Acid-Base Disorders and Appropriate Compensations

Disorder	Appropriate Compensation
Acute respiratory acidosis (pH 7.40, $Pa{CO_2}$ >40 mm Hg)	$0.1 \times \Delta Pa{CO_2} \pm 3 = \Delta[HCO_3^-]$
Acute respiratory alkalosis (pH 7.40, $Pa{CO_2}$ <40 mm Hg)	$0.1 \times \Delta Pa{CO_2} \times (1\text{-}3) = \Delta[HCO_3^-]$
Metabolic alkalosis (pH >7.40, $[HCO_3^-]$ >24 mEq/L)	$\Delta[HCO_3^-] \times (0.8) = \Delta Pa{CO_2}$
Metabolic acidosis (pH <7.40, $[HCO_3^-]$ <24 mEq/L)	$\Delta[HCO_3^-] \times (12) = \Delta Pa{CO_2}$

- Perform arterial or venous blood gas analyses (or both) in the proper clinical setting (eg, apnea, agitation, profound hypotension). Most blood gas laboratories measure pH and Pa_{CO_2} directly and calculate bicarbonate based on the Henderson or Henderson-Hasselbalch equation; therefore, if time permits, performing simultaneous plasma bicarbonate determination may be more accurate when checking for appropriate compensatory changes.

- Assess the pH level: pH levels between 7.35 and 7.45 may be considered normal, but for the interpretation of an acid-base disorder, a pH of more than 7.40 is considered alkalemic and a pH less than 7.40 is considered acidemic.

- Determine whether the primary disorder is metabolic or respiratory. If the pH is 7.30, the patient has at least a metabolic or respiratory acidosis. If the bicarbonate level is less than 24 mEq/L, the primary disorder is a metabolic acidosis. If the Pa_{CO_2} is more than 40 mm Hg, the primary disorder is a respiratory acidosis. (If the serum bicarbonate level is <24 mEq/L and the Pa_{CO_2} is >40 mm Hg, obviously metabolic and respiratory acidoses exist.)

- Determine the magnitude of compensation based on one of the following guidelines:
  For acute respiratory acidosis:
  $\Delta[HCO_3^-] = 0.1 \times \Delta Pa_{CO_2} \pm 3$.

  For acute respiratory alkalosis:
  $\Delta[HCO_3^-] = 0.1 \times \Delta Pa_{CO_2} \times (1\text{-}3)$.

  For metabolic alkalosis:
  $\Delta Pa_{CO_2} = \Delta[HCO_3^-] \times (0.8)$.

  For metabolic acidosis:
  $\Delta Pa_{CO_2} = \Delta[HCO_3^-] \times (1.2)$.

- If compensation is not appropriate, determine the secondary problem. For example, a postoperative patient recovering from general anesthesia for major abdominal surgery has a pH of 7.20, a bicarbonate concentration of 18 mEq/L, and a Pa_{CO_2} of 38 mm Hg in the PACU. This patient has an obvious acidosis, and because his bicarbonate concentration is less than 24 mEq/L, there must be a metabolic acidosis. However, the appropriate

degree of hyperventilation for this degree of metabolic acidosis should be 6 × 1.2, or a decrease in Pa_{CO_2} of 7 mm Hg to a Pa_{CO_2} of 33 mm Hg. Therefore, this patient has an inappropriate respiratory response and appears to be hypoventilating relative to the severity of the metabolic acidosis. In other words, the patient has both a primary metabolic acidosis and a secondary respiratory acidosis (although the Pa_{CO_2} is <40 mm Hg).

- Check for the presence or absence of an anion gap.
- Establish a differential diagnosis based on the acid-base disorder.
- Initiate treatment when appropriate.

SUMMARY

- Acute respiratory acidosis: acidosis defined as a pH less than 7.40 and a Pa_{CO_2} more than 40 mm Hg. Compensation relies on titration of intracellular nonbicarbonate buffers and so-called chloride shift. An appropriate increase in serum bicarbonate would be based on the following formula: $\Delta[HCO_3^-] = 0.1 \times Pa_{CO_2} \pm 3$.

- Acute respiratory alkalosis: alkalosis defined as a pH more than 7.40 and a Pa_{CO_2} less than 40 mm Hg. Compensation relies on renal excretion of bicarbonate and a decrease in titratable acid excretion. An appropriate decrease in serum bicarbonate would be based on the following formula: $\Delta[HCO_3^-] = 0.1 \times Pa_{CO_2} \times (1\text{-}3)$.

- Metabolic alkalosis: alkalosis defined as a pH more than 7.40 and $[HCO_3^-]$ more than 24 mEq/L. Appropriate compensation relies upon a degree of alveolar hypoventilation based on the following equation: $\Delta Pa_{CO_2} = [HCO_3^-] \times (0.8)$.

- Metabolic acidosis: acidosis defined as a pH less than 7.40 and HCO_3^- less than 24 mEq/L. Appropriate compensation relies primarily on alveolar hyperventilation based on the following equation: $\Delta Pa_{CO_2} = \Delta[HCO_3^-] \times (1.2)$.

- Hyperchloremia: Excess of chloride defined as a serum Na^+:Cl^- ratio less than 1.36:1. This ratio is also useful for determining whether an IV solution

is itself hyperchloremic. For example, a liter of Ringer's lactate has a [Na^+] of 130 mEq/L and a [Cl^-] of 109 mEq/L for a ratio of 1.19. This solution is therefore hyperchloremic in nature.

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CHAPTER 35

Electrolyte and Metabolic Abnormalities

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Key words: water balance, sodium metabolism, homeostasis, potassium, calcium, magnesium, phosphorous

Electrolyte and metabolic abnormalities are among the most common problems encountered by practitioners caring for critically ill patients. This chapter focuses on abnormalities in the metabolism of sodium, potassium, calcium, magnesium, and phosphorus. Even subtle derangements in the measured levels of these electrolytes may have implications for total body homeostasis and organ function.

ABNORMALITIES OF SODIUM METABOLISM

Abnormalities of the serum sodium concentration ([Na^+]) are common in critically ill patients. Frequently, these abnormalities are asymptomatic, but when symptoms occur, they range from minor to life-threatening. Therefore, management should be individualized. The risk of treatment must be balanced against the risk of the abnormality. The normal daily sodium requirement is 1 to 2 mEq/kg per 24 hours.

Relationship Between Abnormalities of Water Balance and Sodium Metabolism

Changes in the extracellular solute concentration reflect changes in the total body water (TBW) content. Since sodium is the primary extracellular cation, it is the principal determinant of extracellular solute concentration. Therefore, [Na^+] reflects TBW content. Changes in TBW content cause inversely proportional changes in [Na^+]. The clinical implication is that abnormalities in [Na^+] are indicative of abnormal TBW content. From a practical standpoint, this means

that [Na^+] reflects the tonicity of body fluids, not total body sodium content. In other words, abnormal [Na^+] indicates a water problem, not a sodium problem. Of course, there are conditions in which total body sodium is abnormal, but these are rare compared with the conditions in which TBW is abnormal.

Hyponatremia

Hyponatremia is defined as [Na^+] less than 135 mEq/L and is the most common electrolyte abnormality encountered in clinical medicine. Hyponatremia occurs in 2% to 4% of hospitalized patients and in 30% of ICU patients. Mortality may be up to 50% in acute hyponatremia and 10% to 15% in chronic hyponatremia. These mortality rates reflect the morbidity of the underlying disorder rather than mortality attributed solely to the abnormal [Na^+].

Dilutional hyponatremia is the most common subtype of hyponatremia, particularly in hospitalized patients. With this condition, an excess of water relative to sodium occurs because water excretion by the kidney is impaired or solute-free water intake is excessive. In this condition, the serum chloride concentration [Cl^-] is usually normal. In those less common instances in which true total body sodium depletion results in hyponatremia, the [Cl^-] is usually low.

When the broad diagnosis of hyponatremia is considered, an algorithmic approach to classification leads to a rational method of evaluation and management. The first step is determination of serum osmolality. Hyponatremia is usually associated with hypo-osmolality (<280 mOsm/kg H_2O).

Pseudohyponatremia occurs when serum osmolality is normal (280-320 mOsm/kg H_2O). The most common scenarios are hyperlipidemia and hyperproteinemia. The solid phase of plasma is increased when large quantities of lipids or proteins are present. An increase in plasma lipids of 4.6 g/L or plasma protein concentrations greater than 10 g/dL decreases the [Na^+] by 1 mEq/L. This is an artifact of the technology used to measure [Na^+].

Translocational hyponatremia occurs with hyperosmolality (>320 mOsm/kg H_2O). Water moves from the intracellular space to the extracellular space in the presence of osmotically active solutes. Altered [Na^+] does not reflect a change in TBW. This most frequently occurs with hyperglycemia. The [Na^+] decreases 1.6 mEq/L for every 100 mg/dL increase in plasma glucose concentration; when severe hyperglycemia is present (>500 mg/dL), the correction factor should be

2.4. Translocational hyponatremia is also associated with hypertonic sodium-free solutions, such as mannitol, glycine, or maltose.

After it has been determined that hyponatremia is indeed hypo-osmolar, assessment of volume status and urine sodium concentration reveals additional specific causes of hyponatremia.

Hypo-osmolar Hypovolemic Hyponatremia

This type of hyponatremia results when a TBW deficit occurs in conjunction with a greater degree of total body sodium deficit. These patients are clinically volume depleted. Typical signs on physical examination include tachycardia, orthostatic hypotension, flattened neck veins, dry mucous membranes, and decreased skin turgor. When the urine sodium concentration is greater than 20 mmol/L, renal losses are the origin of hyponatremia in this subclassification. Specific diagnoses include diuretic excess, deficiency of mineralocorticoids, cerebral salt wasting, bicarbonaturia (renal tubular acidosis and metabolic alkalosis), ketonuria, and osmotic diuresis. When the urine sodium concentration is less than 20 mmol/L, extrarenal losses are the cause of hyponatremia in this subclassification. Examples include vomiting, diarrhea, and “third spacing” (as occurs in burns, pancreatitis, and trauma).

Identification and treatment of the underlying cause of fluid loss are the first priorities. Volume resuscitation with an isotonic resuscitative solution is also important in management.

Hypo-osmolar Euvolemic Hyponatremia

This entity occurs when TBW is increased and total body sodium is normal. This is the most common subcategory of hyponatremia and includes dilutional hyponatremia. Edema is absent in these patients, and urine sodium concentration is typically greater than 20 mmol/L. Causes include glucocorticoid deficiency, hypothyroidism, stress, many medications (vasopressin analogs, drugs that enhance vasopressin release, drugs that potentiate renal action of vasopressin, and numerous drugs with an unknown mechanism for hyponatremia, including haloperidol, amitriptyline, and other psychotropic medications), and the syndrome of inappropriate antidiuretic hormone (ADH) secretion.

The syndrome of inappropriate ADH secretion is a diagnosis of exclusion, necessitating the fulfillment of specific criteria to establish the diagnosis. Plasma osmolality must be less than 270 mOsm/kg H_2O; urine osmolality must be

greater than 100 mOsm/kg H_2O; the patient must be euvolemic; the urine sodium concentration must be elevated; adrenal, thyroid, pituitary, and renal insufficiency must be absent; and diuretic use must be absent.

Identification and treatment of the underlying cause are the first treatment priorities in this subcategory of hyponatremia. Free water restriction is also a mainstay of therapy. If urine osmolality is high, a loop diuretic or demeclocycline and administration of additional salt may be effective.

When one is considering treatment of this subcategory of hyponatremia, the topic of aquaporins and vaptans must be reviewed. The relationship of aquaporins to the physiological effects of ADH has been the subject of much investigation. Aquaporins are proteins embedded in the cell membrane that regulate the flow of water and as such are functional water channels or "water pores." Many of the identified aquaporins in mammals are located in the kidney. Principal cells lining the renal collecting ducts help to control body water homeostasis by regulating water resorption through aquaporin 2 (AQP2), aquaporin 3 (AQP3), and aquaporin 4 (AQP4). ADH binds to the vasopressin 2 (V2) receptor on the basal membrane of the renal collecting duct. In doing so, ADH adjusts the quantity of AQP2 in the plasma membrane by triggering its redistribution from intracellular vesicles into the apical plasma membrane. ADH renders the renal collecting duct highly permeable to water, which enters the cells via AQP2 on the apical plasma membrane and exits through AQP3 and AQP4, located on the basolateral plasma membrane. Vaptans are nonpeptide V2 antagonists, which counteract the effect of ADH on the renal collecting ducts. Conivaptan is a mixed V2/V1a antagonist approved by the US Food and Drug Administration for intravenous use in the treatment of euvolemic and hypervolemic hyponatremia. This drug induces a dose-dependent, electrolyte-sparing aquaresis (solute-free water excretion), thereby increasing [Na^+], free water clearance, urine flow, and plasma osmolality. However, experience with vaptans in critically ill patients is not well established. Use should be limited to refractory cases and should be closely monitored.

Hypo-osmolar Hypervolemic Hyponatremia

This entity occurs when TBW is markedly increased relative to a lesser degree of increase in total body sodium. These patients are typically edematous. When the urine sodium concentration is greater than 20 mmol/L, the most common cause is acute or chronic renal failure. When the urine sodium concentration is less than 20 mmol/L, nephrotic syndrome, hepatic cirrhosis, or cardiac failure are

likely causes and are characterized by a decreased effective arterial blood volume. This is mediated by hypoalbuminemia in nephrotic syndrome, by peripheral vasodilation in cirrhosis, and by diminished cardiac output in cardiac failure. The derangement in effective circulating blood volume results in increased angiotensin II, increased vasopressin, and increased sympathetic stimulation, all of which promote renal sodium and water retention.

The mainstay of treatment is management of the underlying cause of decreased effective circulating volume. Salt and water restriction are important. Loop diuretics may be indicated in some patients. As in the management of refractory hypo-osmolar euvolemic hyponatremia, vaptans may be of benefit in selected and closely monitored patients.

Treatment of Symptomatic Hyponatremia

Hyponatremia creates an osmolar gap, which causes water to move from the extracellular space to the intracellular space, which in turn results in cell swelling. Cerebral edema, therefore, results in the neurological symptoms associated with hyponatremia: nausea, emesis, lethargy, confusion, coma, seizures, cerebral herniation, and death.

Treatment is based on the presence or absence of symptoms and whether the hyponatremia is acute (develops in <48 hours) or chronic (develops over the course of >48 hours). Treatment should be undertaken with caution and closely monitored to minimize the possibility of osmotic demyelination syndrome (otherwise known as central demyelination syndrome, central pontine demyelination syndrome, and central pontine myelinolysis). This complication is most likely to occur with therapy for chronic hyponatremia as a result of aggressive and rapid overcorrection, including large concentration corrections (>12-15 mEq/L per 24 hours) and rapid concentration changes (>1-2 mEq/L/h). Patient populations at highest risk include alcoholics; people with protein-calorie malnutrition, hypokalemia, or thermal injury; and elderly women taking thiazide diuretics. Generalized encephalopathy occurs first. Two to 3 days after the [Na^+] is corrected, classic symptoms are noted: behavioral changes, cranial nerve palsies, and quadriplegia. Diagnostic lesions on magnetic resonance imaging may take 2 weeks after onset of symptoms to develop.

The systemic treatments described in the preceding sections pertain to patients who are neurologically asymptomatic. In general, all patients with neurologically symptomatic hyponatremia should be specifically treated with

sodium repletion. The sodium deficit is calculated as follows:

$$\text{Sodium Deficit} = 0.5 \times \text{Lean Body Weight} \times (120 - \text{Measured } [Na^+]).$$

A 3% NaCl infusion is used to correct the sodium deficit. Serum electrolytes should be checked every 4 to 6 hours, and the neurological examination should be repeated frequently. The rapidity of correction should be proportional to the rapidity of onset. Acute symptomatic hyponatremia is corrected more quickly than chronic symptomatic hyponatremia. The rate of correction of acute symptomatic hyponatremia is less than or equal to 2 mEq/L/h and less than or equal to 15 mEq/L in the first 24 hours. The rate of correction of chronic symptomatic hyponatremia is less than or equal to 1.5 mEq/L/h and less than or equal to 12 mEq/L in the first 24 hours. If urine osmolality is high, a loop diuretic may be used as well as 3% NaCl. This is particularly true in cases of dilutional hyponatremia.

Hypernatremia

Hypernatremia is defined as $[Na^+]$ greater than 145 mEq/L. It occurs in 2% of hospitalized patients and in 15% of ICU patients. Mortality rates may approach 70%. The underlying pathophysiological process is attributed to either free water deficit or total body sodium excess. As is the case with hyponatremia, an algorithmic approach is useful to identify specific causes and management strategies for the broad category of hypernatremia.

Hypovolemic Hypernatremia

This entity is characterized by a TBW deficit and a lesser degree of total body sodium deficit. The patients are clinically hypovolemic, manifested by tachycardia, orthostatic hypotension, flat neck veins, dry mucous membranes, and decreased skin turgor. When urine sodium concentration is greater than 20 mmol/L, renal losses are most likely. Causes include diuretic excess, postobstructive uropathy, and intrinsic renal disease. When urine sodium concentration is less than 20 mmol/L, extrarenal losses are usually the culprit. Causes include excessive sweating, burns, diarrhea, and fistulas. Treatment includes correction of the volume deficit with isotonic fluid as well as correction of the free water deficit (discussed subsequently). Identification of and correction of the cause of the losses are integral to treatment.

Euvolemic Hypernatremia

This entity is characterized by a decrease in TBW and normal total body sodium. These patients are typically not edematous. The urine sodium concentration is variable and depends on the patient's water intake. Renal losses include diabetes insipidus and hypodipsia. Extrarenal losses include insensible losses (respiratory and dermal).

Treatment includes correction of the free water deficit (discussed subsequently). Long-term therapy may be necessary for central diabetes insipidus (desmopressin) and nephrogenic diabetes insipidus (thiazide diuretics, nonsteroidal anti-inflammatory drugs, amiloride).

Hypervolemic Hypernatremia

This is the least common subtype of hypernatremia. Total body sodium is increased to a greater degree than TBW. Urine sodium concentration is typically greater than 20 mmol/L. Causes include excessive sodium intake (treatment with 3% NaCl, NaCl tablets, hypertonic $NaHCO_3$), primary hyperaldosteronism, Cushing syndrome, and hypertonic dialysis.

Treatment includes removal of the excess sodium. Furosemide diuresis is used to manage the excess volume. Hemodialysis is used if indicated in those patients with renal failure.

Treatment of Symptomatic Hypernatremia

Neurological symptoms associated with hypernatremia include confusion, weakness, and lethargy progressing to seizures, coma, and death. Correction of hypernatremia should be undertaken cautiously, since cerebral edema may occur if correction occurs too rapidly. The rapidity of correction of hypernatremia should be proportional to the rapidity of onset. Water repletion is the cornerstone of treatment. The free water deficit is calculated as follows:

$$\text{Free Water Deficit} = (0.6 \times \text{Total Body Weight}) \times \left[(\text{Measured } [Na^+]/140) - 1\right].$$

Half the calculated deficit is replaced in the first 12 to 24 hours, no more rapidly than 2 mEq/L/h. The second half of the deficit is replaced over the ensuing 48 hours.

ABNORMALITIES OF POTASSIUM METABOLISM

Potassium is the most abundant intracellular cation. Hypokalemia and hyperkalemia are common in hospitalized patients. Critically ill patients are at especially high risk of developing complications from altered serum potassium concentration [K^+]. The normal daily potassium requirement is 0.25 to 0.50 mEq/kg per 24 hours.

Hypokalemia

Most hypokalemic patients are asymptomatic; in patients who experience symptoms, cardiac and neuromuscular abnormalities are the most common manifestations. Abnormal cardiac electrical activity progressing to cardiac arrest occurs in hypokalemic patients with underlying cardiac disease or those taking digitalis. Progressive worsening of hypokalemia results in a characteristic deterioration of electrocardiographic (ECG) changes: flat T waves, ST depression, U waves, QT interval prolongation, and ventricular arrhythmias.

Musculoskeletal symptoms include generalized weakness, which can progress to muscle necrosis and rhabdomyolysis. Ascending muscle paralysis can result in respiratory failure and arrest.

Numerous conditions have been identified as causes of hypokalemia. Inadequate intake should always be considered. Increased potassium excretion occurs via gastrointestinal or renal losses. Gastrointestinal losses include diarrhea, overuse of laxatives, and enema abuse. Renal losses can occur spontaneously or can be pharmacologically induced. Diuretics (loop and thiazides) are the most common cause of hypokalemia in hospitalized patients. Additional causes of renal loss include metabolic alkalosis, osmotic diuresis (hyperglycemia), mineralocorticoid excess (primary hyperaldosteronism, congenital adrenal hyperplasia, glucocorticoid-responsive aldosteronism), penicillin and its synthetic derivatives, hypomagnesemia (caused by aminoglycosides, amphotericin B, cisplatin, foscarnet), high-dose glucocorticoids, and renal tubular acidosis (type 1 and some type 2). Miscellaneous causes of renal potassium loss include Liddle disease, Bartter syndrome, and congenital enzyme deficiencies. Shift of potassium into cells is another broad category of causes of hypokalemia. Drugs that cause this phenomenon include β-adrenergic agonists (bronchodilators, decongestants, tocolytics), insulin, theophylline, caffeine, and barium poisoning. Clinical conditions that cause hypokalemia by this mechanism include delirium tremens (increased endogenous β-adrenergic stimulation), hyperthyroidism, and

familial hypokalemic periodic paralysis. Finally, dilution should be considered as a cause of hypokalemia, although this is rarely the sole cause.

Potassium supplementation is the treatment for hypokalemia. Either potassium chloride or potassium phosphate is used. [K^+] decreases by 0.3 mEq/L for each 100-mEq decrease in total body potassium. Potassium repletion is given orally or intravenously, depending on the clinical circumstances and degree of hypokalemia. Treatment for [K^+] less than 3.0 mEq/L is IV repletion in a monitored setting, given the risk of dysrhythmia during repletion. Hypomagnesemia should also be corrected, because hypomagnesemia promotes renal loss of potassium. Magnesium repletion of 8 to 10 g is often required to correct [K^+] less than 3.0 mEq/L. Once [K^+] has decreased to less than 3.0 mEq/L, the quantity of potassium repletion required for correction is nonlinear; a minimum of 100 mEq of potassium is required to restore normal concentrations.

Hyperkalemia

Hyperkalemia is defined as [K^+] greater than 5.0 mEq/L. Pseudohyperkalemia occurs with marked leukocytosis or thrombocytosis and from hemolysis of a blood specimen. A serum potassium concentration (clotted) 0.2 to 0.3 mEq/L greater than a plasma potassium concentration (unclotted) indicates pseudohyperkalemia.

Mild hyperkalemia is usually asymptomatic. As is the case with hypokalemia, when symptoms occur, manifestations are usually cardiac and neuromuscular. Characteristic ECG changes include peaked T waves, widening of the QRS complex, AV conduction blocks, sine waves, ventricular fibrillation, and asystole. With respect to neuromuscular symptoms, paresthesias and weakness of the extremities may progress to symmetrical flaccid paralysis, ascending to the trunk and involving the respiratory muscles. The cranial nerves are characteristically spared.

Three distinct mechanisms may cause hyperkalemia: (1) excessive potassium administration, (2) impaired potassium excretion, and (3) shift of potassium out of cells. Renal failure is the most common specific cause of impaired potassium excretion. Other causes of impaired potassium excretion include mineralocorticoid deficiency (Addison disease, type 4 renal tubular acidosis, heparin-induced inhibition of aldosterone synthesis, hereditary enzyme deficiencies); pseudohypoaldosteronism (chronic kidney failure in diabetes mellitus and tubulointerstitial disease); drugs (potassium-sparing diuretics,

angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, trimethaphan, cyclosporine, tacrolimus, pentamidine, trimethoprim, azole antifungals, fluoride, herbal supplements, penicillin G potassium); and ureterojejunostomy (via increased jejunal resorption of urinary potassium). Shift of potassium out of cells is caused by hypertonicity; tissue destruction (rhabdomyolysis, burns, trauma); cellular destruction (tumor lysis, acute intravascular hemolysis); drugs (β-adrenergic blockers, digoxin, succinylcholine, lysine, and arginine amino acids); familial hyperkalemic periodic paralysis; and insulin deficiency or resistance.

Worth mentioning are the effects of acidosis on [K^+]. Traditionally, it was thought that an inverse relationship between serum pH and [K^+] existed. However, this has been disproven. The effects of acidosis on [K^+] are complex and incompletely understood.

Patients with [K^+] greater than 6.5 mEq/L or ECG changes consistent with hyperkalemia should be treated emergently. Five treatment modalities are typically used in the acute situation:

- Renal excretion of potassium: plasma volume expansion followed by a potassium-wasting diuretic (ie, furosemide).
- Direct antagonism of the hyperkalemic effect on cell membrane polarization (cardiac cell membrane stabilization): calcium chloride.
- Movement of extracellular potassium into the intracellular compartment: regular insulin plus glucose, albuterol, sodium bicarbonate (as alluded to previously, this is controversial), aminophylline.
- Gastrointestinal excretion of potassium: sodium polystyrene sulfonate.
- Extracorporeal removal of potassium: intermittent hemodialysis or continuous renal replacement therapy (depending on hemodynamic status).

Most patients receive treatments 1 through 4. Extracorporeal treatments are typically necessary only in those with renal impairment or preexisting dialysis requiring renal failure. Rarely, patients with normal kidneys may benefit from acute hemodialysis for rapid lifesaving potassium removal.

ABNORMALITIES OF CALCIUM METABOLISM

Total serum calcium ranges from 9.4 to 10.0 mg/dL. The prevalence of hypocalcemia in the ICU ranges from 70% to 90% when total serum calcium is measured. This decreases to 15% to 50% when ionized calcium is measured. These values reflect the prevalence of hypoalbuminemia in the critically ill patient population. Studies have found that in critically ill patients, formulas for correction for hypoalbuminemia do not correlate with measures of ionized calcium; therefore, if hypocalcemia is suspected to be significant, an ionized calcium level should be assessed. The ionized calcium is the physiologically active component, as opposed to bound calcium. Hypercalcemia occurs in less than 15% of critically ill patients.

Calcium is a divalent cation involved in a myriad of critical biological processes. Intracellular and extracellular calcium concentrations are tightly regulated. The average adult has 1 to 2 kg of total body calcium localized primarily in bone (99% as hydroxyapatite). Release of calcium from this reservoir is regulated by extracellular calcium concentration as well as the balance between parathyroid hormone (PTH) and calcitonin. Extracellular concentrations of calcium are 10,000 times greater than intracellular concentrations.

Hypocalcemia

Hypocalcemia is defined as an ionized calcium level less than 1.0 mmol/L or a total calcium level less than 8.5 mg/dL. Ionized hypocalcemia is common in critically ill patients with sepsis, pancreatitis, or severe trauma or in postoperative patients (especially after large-volume plasma volume expansion with hypocalcemic solutions) and is associated with increased mortality. Circulating cytokines (tumor necrosis factor and interleukin 6) and procalcitonin levels as measurements of systemic inflammation correlate with the degree of hypocalcemia in critically ill patients.

The cause of hypocalcemia in critical illness is usually multifactorial, with multiple interrelated mechanisms contributing. Impaired PTH secretion or action occurs in primary and secondary hypoparathyroidism. Vitamin D deficiency or resistance is especially important in elderly patients; causes include decreased intake, malnutrition, hepatic disease, renal disease, hypomagnesemia, sepsis, and the systemic inflammatory response syndrome. Calcium chelation or precipitation occurs with hyperphosphatemia; citrate administration (in massive blood transfusion); pancreatitis (via saponification of retroperitoneal fat); rhabdomyolysis; ethylene glycol ingestion; and alkalosis (increased binding of calcium to albumin). Finally, impaired mobilization of calcium from bone occurs

in hypothyroidism; calcitonin excess; and administration of cisplatin, diphosphonate, mithramycin, and phosphate.

Hypocalcemia is frequently asymptomatic, but when symptoms do occur, the cardiovascular and neuromuscular systems are most frequently involved. Cardiovascular effects include decreased cardiac output and hypotension refractory to vasopressors and plasma volume expansion. Cardiac dysrhythmias include ventricular tachycardia, prolonged QT interval, and complete heart block. Neurological symptoms include paresthesias and seizures. Neuromuscular symptoms include muscle spasms and tetany. Chvostek sign is involuntary twitching of the facial muscles when the facial nerve is lightly tapped; it is present in 10% to 25% of normal adults and may be absent in chronic hypocalcemia. Trousseau sign is carpopedal spasm in response to decreased blood flow to the hand (a blood pressure cuff is inflated to 20 mm Hg for 3 minutes); it is absent in one-third of patients with hypocalcemia. Psychiatric disturbances include dementia, psychosis, and depression.

Severe ionized hypocalcemia (<0.8 mmol/L) and symptomatic hypocalcemia are indications for treatment. Intravenous calcium repletion includes calcium gluconate and calcium chloride. For symptomatic patients and especially for those with cardiac dysrhythmias, calcium chloride is preferred because the calcium is physiologically immediately available. Calcium gluconate requires hepatic degluconation to provide biologically usable calcium.

Hypercalcemia

Hypercalcemia is defined as a serum calcium level greater than 10.4 mg/dL. This disorder is rare in critically ill patients. The cause is typically excessive bone resorption associated with prolonged immobility, paraneoplastic syndromes, and hyperparathyroidism. Hyperparathyroidism and humoral hypercalcemia of malignancy are the most common causes of hypercalcemia in hospitalized patients. Sarcoidosis and medications (particularly thiazide diuretics) are additional causes.

Mild hypercalcemia is asymptomatic. Levels greater than 12 mg/dL produce neuropsychiatric symptoms including confusion, delirium, psychosis, and coma. Gastrointestinal symptoms include nausea, emesis, constipation, abdominal pain, and ileus. Cardiovascular symptoms are characterized by hypotension, hypovolemia, and a shortened QT interval. Skeletal muscle weakness may also be present. Patients with levels greater than 14 mg/dL and symptomatic patients

should be treated. Hydration, forced kaliuresis (using furosemide), and management of the underlying cause are the cornerstones of treatment. When underlying malignancy is present, salmon calcitonin, pamidronate, or plicamycin (inhibitors of bone resorption) may be necessary. Rarely, hemodialysis may be of benefit in the acute setting. Parathyroidectomy is generally reserved for failure of medical therapy and is only rarely used in the acute setting.

ABNORMALITIES OF MAGNESIUM METABOLISM

Magnesium is a divalent cation and is the second most abundant intracellular cation after potassium. Magnesium is integral to sodium, potassium, and calcium homeostasis and is an essential cofactor for metabolism requiring adenosine triphosphate. Total body magnesium is 20 to 28 g, distributed in bone, muscle, soft tissue, and blood. Notably, only 0.8% occurs in the blood. Normal serum magnesium concentration is 1.5 to 2.3 mg/dL; 67% is ionized, which is the physiologically active form. However, ionized magnesium is not typically measured in the clinical laboratory. Hypoalbuminemia is associated with decreased total magnesium, but the ionized fraction may remain normal.

No hormonal mechanisms have been identified for the regulation of magnesium. Homeostasis is maintained by intestinal absorption, renal resorption, and bone mobilization.

Hypomagnesemia

The incidence of hypomagnesemia in critically ill patients has been cited from 15% to 60%. Numerous causes have been identified. Inadequate magnesium intake is one category. Renal losses comprise a second category, which includes diuretic use. Magnesium resorption in the kidney is inversely related to urine flow, which is the mechanism of hypomagnesemia related to diuretics. Also contributing to renal losses are alcohol abuse; diabetes; acute tubular necrosis; and administration of aminoglycoside, amphotericin, cyclosporine, cisplatin, or digoxin. Gastrointestinal losses comprise a third category and include vomiting, diarrhea, nasogastric suction, and pancreatitis. Acute intracellular shift of magnesium is the fourth category and is associated with refeeding (glucose or amino acids), insulin administration, excessive catecholamines, and metabolic acidosis. The fifth category comprises miscellaneous clinical entities, including burns, massive blood transfusion, cardiopulmonary bypass, hepatic transplantation, severe sepsis, and dilution (large-volume plasma volume expansion). Of the myriad causes identified, the most common conditions

associated with hypomagnesemia are diuretic use, hepatic transplantation, severe sepsis, and large-volume plasma volume expansion.

Of particular note, hypomagnesemia is usually identified in conjunction with hypokalemia, hypocalcemia, and hypophosphatemia. Hypocalcemia and hypokalemia are refractory to correction unless magnesium is also repleted.

Hypomagnesemia is frequently asymptomatic. When symptoms occur, the cardiovascular, metabolic, and neuromuscular systems are affected. Symptoms and ECG changes parallel changes associated with hypocalcemia and hypokalemia, respectively. With respect to cardiac symptoms, atrial fibrillation or flutter as well as ventricular tachycardia (in particular, torsade de pointes) may occur. Seizures may also occur. Magnesium depresses the seizure threshold by competitively inhibiting *N*-methyl-D-aspartate receptors and is used in the management of preeclampsia and eclampsia. Magnesium may also be used to treat bronchospasm in asthmatic patients because of its relaxant effects on smooth muscle.

Intravenous magnesium (magnesium sulfate, $MgSO_4$) is used for magnesium repletion in critically ill patients. For torsade de pointes, 1 to 2 g of $MgSO_4$ is administered as a bolus over 5 minutes. Specific dosing regimens are individualized for routine repletion. Many ICUs have developed sliding-scale repletion regimens, similar to those used for automatic potassium repletion.

Hypermagnesemia

Hypermagnesemia occurs primarily in patients with renal failure and with excessive intake. Symptoms may occur with levels greater than 4.0 mg/dL. The musculoskeletal, neurological, and cardiac systems are affected. Decreased deep tendon reflexes may progress to muscle paralysis, including respiratory depression. Lethargy and somnolence may occur. Bradycardia, hypotension, and complete heart block progressing to cardiac arrest may occur as well.

No specific antidote for hypermagnesemia is available. Intravenous calcium may be useful when hemodynamic instability occurs. Provision of plasma volume expansion coupled with furosemide may enhance renal excretion. Dialysis may be indicated in patients with renal failure and acute magnesium intoxication. Of note, induced hypermagnesemia is very rare in the ICU, with the exception of patients undergoing tocolysis, despite the routine administration of large daily doses (8-10 g).

ABNORMALITIES OF PHOSPHATE METABOLISM

The majority of total body phosphorus is found in the bones as hydroxyapatite, as is true for calcium. Unlike calcium, however, the majority of phosphate is intracellular. Phosphate is an essential component of adenosine triphosphate and of the phospholipids that comprise cell membranes. It is also an important acid-base buffer in physiological systems. Phosphate homeostasis is dependent on bone metabolism (and as such is linked to calcium homeostasis), intestinal absorption, and renal resorption.

Hypophosphatemia

Hypophosphatemia specifically refers to a low serum phosphate concentration and is characterized by degree of severity. Mild is 2.5 to 3.0 mg/dL, moderate is 1.0 to 2.4 mg/dL, and severe is less than 1.0 mg/dL. The term *phosphate depletion* refers to the state of low total body phosphorus stores.

Numerous causes of hypophosphatemia have been identified and fall into 4 general categories. The first is transcellular shift. Perhaps the most important example of this is refeeding syndrome, which occurs when the abrupt initiation of carbohydrate causes an insulin spike after a period of starvation, which in turn increases cellular phosphate uptake. Similarly, exogenous administration of insulin can result in the same physiological process, and respiratory alkalosis causes a similar shift. The second category is renal loss. Pharmacological administration of diuretics and osmotic diuresis in diabetic ketoacidosis are examples. Also included in this category are hyperparathyroidism (primary or secondary), which decreases urinary resorption of phosphate, and proximal renal tubular dysfunction, as occurs in Fanconi syndrome. The third category entails insufficient intestinal absorption, which occurs with malnutrition, the administration of phosphate-binding antacids, vitamin D deficiency, chronic diarrhea, nasogastric suction, and malabsorption. Fourth, extreme catabolic states can cause total-body phosphate depletion. Included in this group of disease entities are burns, trauma, and sepsis.

Hypophosphatemia becomes symptomatic with severe depletion. Complications attributable to the musculoskeletal system include diffuse skeletal muscle weakness, rhabdomyolysis, and bone demineralization. Acute and chronic respiratory failure secondary to diaphragmatic weakness has been associated with failure in ventilator weaning. Neurological complications include confusion, lethargy, gait disturbance, and paresthesias. Hematological

manifestations include acute hemolytic anemia and leukocyte dysfunction. Cardiovascular manifestations may include acute left ventricular dysfunction and a reversible dilated cardiomyopathy.

Severe hypophosphatemia is repleted intravenously, using either sodium phosphate or potassium phosphate, depending on the electrolyte milieu. Caution should be observed in patients with renal failure and those who are hypercalcemic (at risk of metastatic calcification).

Hyperphosphatemia

Hyperphosphatemia is defined as a serum phosphate level greater than 4.5 mg/dL. Renal failure and excessive administration are the most common causes. Increased renal resorption occurs in hypoparathyroidism and thyrotoxicosis. Extensive cell damage can also cause hyperphosphatemia and may occur with rhabdomyolysis, tumor lysis syndrome, and hemolysis. Laxative abuse and bisphosphonate therapy are also causes.

Clinical symptoms are frequently related to hypocalcemia. Hyperphosphatemia causes hypocalcemia by precipitating calcium, interfering with PTH, and decreasing vitamin D levels.

The primary treatment for acute hyperphosphatemia is augmentation of renal excretion using plasma volume expansion coupled with diuresis (particularly acetazolamide). Dialysis may be required in some instances. Oral phosphate binders are used in patients who have chronic renal failure. Oral binders also can be used in patients with acute renal failure who are receiving enteral nutrition with a high phosphate concentration in order to avoid hyperphosphatemia when the formula cannot be changed without sacrificing optimization of protein administration. This is a relatively common scenario in the ICU.

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CHAPTER 36

Hyperglycemia, Hypoglycemia, and Acute Diabetic Emergencies

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Key words: diabetes mellitus, diabetic ketoacidosis, hyperosmolar hyperglycemic state, hypoglycemia, glycemic variability

HYPERGLYCEMIA IN THE ICU

Clinicians in the ICU commonly encounter patients with metabolic disturbances, including patients who are known to have diabetes mellitus (DM), patients with undiagnosed DM, and patients who have stress-induced hyperglycemia. Mechanisms that explain the underlying pathophysiological process of metabolic disturbances include, but are not limited to, insulin resistance, absolute or relative insulin deficiency, impaired glucose metabolism, and the effects of nutritional supplements or stress-induced hormones such as glucagon and corticosteroids.

Early research on patients with cardiovascular disease and hyperglycemia suggested that insulin might itself be atherogenic, considering that most patients with DM were at high risk for vascular complications. Current literature suggests that glycemic variability, more than insulin resistance or hyperinsulinemia of diabetes, plays a major role in exaggerated inflammatory and oxidative reactions that lead to endothelial disruption and cardiovascular damage.

Initial studies on the effects of hyperglycemia in critically ill patients were focused on DM and its effect on patients with coronary artery disease who required cardiac surgery. Multiple studies have shown that short- and long-term mortality rates following myocardial infarction are significantly higher when hyperglycemia is present, with or without diagnosed DM. It is now believed that

hyperglycemia, rather than the presence of DM, influences morbidity and mortality risk. Stress-induced hyperglycemia (SIH) is also associated with poor outcomes and increased rates of congestive heart failure and cardiogenic shock, especially when encountered during hospitalization for perimyocardial infarction. Regardless of the cause of high blood glucose (BG) levels, patients with BG levels of 200 mg/dL or more have greater mortality risk at 180 days.

Studies have repeatedly demonstrated worsening morbidity and mortality rates in patients with hyperglycemia in all types of ICUs, even for patients with only modest elevations of mean glucose levels during their ICU stays. Poorly controlled hyperglycemia during cardiac surgery was associated with a higher incidence of deep wound infections and subsequently higher mortality rates in the ICU. Further, hyperglycemia, specifically on the first and second postoperative days, was found to be the single most important predictor of serious infection and complications. In other studies, general surgery and medical ICU patients also displayed increased infection rates with hyperglycemia. Additionally, intravenously administered insulin infusions aimed at keeping patients in normoglycemic ranges independently reduced mortality and deep wound infections in the cardiac surgery population.

Treatment of SIH gained popularity after investigators recognized that the presence of hyperglycemia, even without DM, contributed to poor outcomes in the ICU. After an acute injury, hyperglycemia is likely to be the result of both decreased glucose uptake due to peripheral insulin resistance and increased endogenous glucose production. Hyperglycemia on admission or within the first 2 ICU days is predictive of poor outcomes and higher mortality. Evidence suggests that the cause of hyperglycemia matters more than was historically realized. SIH, compared with hyperglycemia in diabetic patients, was shown to indicate an increased risk of poor outcome in hospitalized patients, including increased length of stay and even mortality. Related to this, studies indicate that a significant percentage of SIH patients are likely to have undiagnosed diabetes. Lack of access to medical care and consequent lack of prior diagnosis and treatment for DM may actually be the main contributing factors to cumulative bad outcomes for individuals with SIH.

Within the group of diabetic patients, the patients with higher preadmission levels of glycated hemoglobin A_{1c} (HbA_{1c}) are reported to have a significantly lower mortality rate compared with those patients with lower HbA_{1c} levels, who are generally considered to have “well-controlled” diabetes. In a recently

published, prospective observational study, Hoang and colleagues (2014) characterized all hyperglycemic patients in a medical ICU according to HbA_{1c} levels, regardless of previous diagnosis of DM. The investigators found that outcomes for diabetic patients were better than the outcomes for nondiabetic hyperglycemic patients. Other studies also suggest a paradox, such that patients with DM, which is a disease known to have associated complications from hyperglycemia, are reported to have a lower risk of postsurgical complications in the setting of hyperglycemia compared with patients without DM. Additionally, Hoang et al reported the prevalence of DM in their "nondiabetic" group to be 13.7% based on HbA_{1c} surveillance. Other investigators previously reported that up to 60% of non-diabetic patients with postoperative hyperglycemia and a myocardial infarction were later diagnosed with DM. Patients may be identified by admission HbA_{1c} monitoring as "likely" to have undiagnosed diabetes or as prediabetic and referred for follow-up after their ICU discharge.

Similarities are found between SIH and gestational diabetes (GD). Both SIH and GD are due to a temporary disorder of glucose homeostasis. Patients with GD should be screened regularly, even after pregnancy, for detection of type 2 DM, as their risk of developing diabetes is higher than that of women who do not have GD during pregnancy. Patients with SIH during an acute illness should also be considered a population at increased risk for developing diabetes, and ideally their HbA_{1c} levels should be monitored as follow-up.

After discovery of the adverse outcomes associated with acute hyperglycemia, studies investigated tight glucose control in the ICU. One of the largest and best known studies in this group was published in 2001 by Van den Berghe and colleagues from Belgium. They investigated 1,548 patients, the majority of whom resided in the surgical ICU following cardiac surgery. These patients were randomized to receive tight versus conventional glucose control regimens; the range for tight or intensive BG control was defined as 80 to 110 mg/dL, and the conventional group was treated if BG was more than 200 mg/dL to maintain BG of 180 to 200 mg/dL. The investigators reported a significant reduction in numerous morbidities and in mortality in the intensive BG group. Van den Berghe et al defined hypoglycemia as BG less than 40 mg/dL and reported low rates of hypoglycemia without adverse effects.

Other randomized controlled studies that followed the first Van den Berghe study failed to show the same mortality benefit, but they consistently demonstrated hypoglycemia as a side effect of tight glycemic control (TGC). These conflicting

results regarding TGC in the ICU led the critical care community to debate what the goal BG target should be during an ICU stay. The largest trial of TGC in ICUs was published as the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) trial. The study randomized 6,104 patients in 42 centers to receive conventional therapy versus intensive insulin therapy (IIT). The results indicated that both mortality and incidence of hypoglycemia were significantly higher in the IIT group.

The use of IIT (ie, tight glucose control) was evaluated in the subgroup of critically ill patients with severe sepsis or septic shock. After the role of corticosteroid therapy was recognized in the Surviving Sepsis Campaign guidelines, treatment of septic shock with steroids became more common. One of the side effects of steroid therapy is hyperglycemia, so the corticosteroid treatment and intensive insulin therapy for septic shock in adults (COIITSS) study investigators evaluated effects of IIT in 509 septic shock patients treated with steroids. Compared with conventional insulin therapy, IIT failed to improve in-hospital mortality among these patients. Similarly, a multicenter randomized controlled trial led by Brunkhorst and colleagues[1], from the SepNet study group, included 537 patients assigned to receive either conventional therapy or IIT after randomization of resuscitation fluids during severe sepsis. Brunkhorst et al concluded that critically ill patients with sepsis who received IIT were in significant danger of hypoglycemia.

In 2015, the American Association of Clinical Endocrinologists and the American College of Endocrinology updated clinical practice guidelines for DM and continued to recommend BG goals of 140 to 180 mg/dL for critically ill patients. Of note, the Society of Critical Care Medicine (SCCM) 2012 guidelines recommend considering initiation of insulin therapy at a BG level of 150 mg/dL with the intent to keep BG levels below 180 mg/dL. The SCCM guidelines also encourage the use of insulin protocols to minimize hypoglycemic episodes, which are defined as BG less than 70 mg/dL. Intravenous insulin infusions remain the preferred method of insulin administration in ICU patients. Of particular note, it is recommended that oral antihyperglycemic agents be discontinued in the hospital setting. Each class of noninsulin antihyperglycemic agents has substantial limitations for inpatient use, leading to this recommendation.

A patient's BG should be monitored frequently to prevent hypoglycemic events. The frequency of BG measures should be specified in nursing protocols, and for patients receiving infusions, BG should be measured at least every 1-2 hours.

Glucose monitoring imposes substantial nursing demands, and nurses need to be well educated on benefits and risks of insulin therapies. Despite ongoing and promising efforts to develop continuous intravenous or arterial glucose sensors for "real-time" measurements of BG with potential closed-loop administration of insulin dosing, these are not yet available commercially.

Additional focus in this arena is on glucose fluctuations or glycemic variability as opposed to a defined target BG range. Several studies report that glycemic variability is associated with poor prognosis. In vitro and animal studies demonstrate that oscillating glucose is worse than a stable constant high glucose, specifically in activating pathways leading to long-term diabetic complications. Glucose fluctuations increase oxidative stress and mitochondrial superoxide production and cause vascular inflammation. In humans, increased free radicals and endothelial dysfunction and risk of hypoglycemia were reported with higher glycemic variability. Further details of these concerns are beyond the scope of this chapter, but future work that aims therapy at limiting glycemic variability may help define better glycemic management strategies for our patients.

ACCURACY OF METHODS FOR BLOOD GLUCOSE MEASUREMENT IN CRITICALLY ILL PATIENTS

The conflicting results of studies on hyperglycemia management in ICUs have raised concerns regarding methods of BG measurement in critically ill patients. Most ICUs use nurse-driven insulin protocols. In ICUs, BG levels are usually measured via bedside glucometry devices, which are point of care testing (POCT) devices. Glucometers have several advantages over laboratory testing; they require only a tiny amount of blood, provide fast results to the bedside care provider, and offer a significant reduction in the costs of frequent BG sampling compared with laboratory analysis.

However, as the 2012 SCCM Guidelines on Use of Insulin Infusions caution, POCT glucometers can yield erroneous results mainly due to the method of the devices, which are dependent on glucose oxidase versus glucose 1 dehydrogenase. For example, high partial pressures of oxygen (PaO_2) can falsely lower BG readings when the glucose oxidase method is being used. Drugs such as acetaminophen, ascorbic acid, dopamine, and mannitol as well as conditions causing hyperbilirubinemia or hyperuricemia may also interfere with the accuracy of POCT, especially those based on the glucose oxidase method. POCT devices with glucose dehydrogenase–based assays can display falsely elevated

results if patients are receiving medications with maltose (eg, immune globulins) or icodextrin (eg, peritoneal dialysis solutions).

Studies that assessed the accuracy of bedside glucometers in ICU settings revealed conflicting results. Capillary and arterial blood samples for BG levels vary both in POCT devices and during blood chemistry analysis. In most reports, capillary blood samples did not correlate with arterial blood sample measurements. In the majority of studies capillary blood sample measurements tended to falsely overestimate BG levels, which can either mask a true hypoglycemic event or lead to increased doses of insulin therapy, thereby increasing risk of hypoglycemia. Other reports suggest that in circulatory shock with hypoperfused capillary beds, increased tissue glucose extraction can result in lower glucose values in capillary samples than in venous samples. In that situation, an underestimation of glucose would cause incorrect diagnosis of hypoglycemia. When patients require vasopressor support during hypotensive stages of their illnesses, with severe peripheral edema or hematocrits below 20% or greater than 50%, capillary sampling for glucose monitoring should be avoided.

Whole BG levels differ from serum samples because the glucose in plasma is approximately 11% higher than in whole blood, given that water content in plasma is higher than in erythrocytes. Therefore, the International Federation of Clinical Chemistry and Laboratory Medicine Protocols recommend a multiplier of 1.11 for conversion of glucose in blood to plasma. In consideration of this fact, some POCT devices are being integrated with this correction factor so that they “self-correct” to promote more accurate BG results.

Anemia is reported to cause incorrect glucose measures by glucometry. Specifically, lower hematocrit values generally allow meters to overestimate BG levels. Glucometers are programmed to assume a normal hematocrit of 40%, and the internal calculation of BG assumes constant displacement of plasma by red blood cells in the sample. Anemic samples containing fewer red blood cells will have less displacement because of an erroneous ratio concentration. This results in a systematic glucose overestimation for anemic samples, which may mask hypoglycemia. Newer glucose meters may address limitations of these older versions.

HYPOGLYCEMIA IN THE ICU

In many studies on TGC, intensive treatment of hyperglycemia in ICUs resulted

in frequent iatrogenic hypoglycemia. Hypoglycemia is defined as a BG level less than 70 mg/dL, and severe hypoglycemia is BG less than 40 mg/dL. Cognitive impairment begins within the 50 to 70 mg/dL BG range. Besides the most severe complications of hypoglycemia (eg, seizure, permanent brain damage, death), there are subtle signs of hypoglycemia such as impaired judgment, headache, confusion, and fatigue that are more challenging to detect in an ICU setting. In multiple trials, hypoglycemia was associated with worse outcomes. Even one episode of severe hypoglycemia is independently associated with increased mortality. In critically ill patients, the severity of the hypoglycemia is associated with higher risk of mortality. It is hard to establish the impact of hypoglycemia on morbidities since concurrent illness and sepsis can increase the risk of cognitive impairment. Guidelines recommend that BG less than 70 mg/dL (<100 mg/dL in neurologically injured patients) be treated immediately with discontinuation of insulin infusion and administration of 10 to 20 g of hypertonic (50%) dextrose, titrated based on the BG value to avoid overcorrection. The BG should be measured after 15 minutes to determine whether additional dextrose is needed. The hypoglycemia treatment goal is to achieve BG greater than 70 mg/dL without inducing iatrogenic hyperglycemia.

Studies of predisposing risk factors for hypoglycemia in critically ill patients have been performed during the past decade. The common risk factors reported are severe sepsis and septic shock, inotropic support, decrease of nutrition without adjustment of insulin infusion, insulin therapy, preexisting diabetes, mechanical ventilation, liver or renal failure, increased severity of illness, and continuous venovenous hemofiltration with bicarbonate-based substitution fluid (**Table 1**). Although no studies have looked specifically into type and route of insulin administration and their correlation with hypoglycemia, subcutaneously administered insulin is speculated to cause stacking of repeated insulin doses, potentially creating risk of hypoglycemia. This is why short-acting analog insulin has replaced regular insulin for subcutaneous therapies. How mechanical ventilation contributes to development of hypoglycemia in the ICU is not clear, but it is hypothesized to be due to the effects of sedation by directly or indirectly increasing risk of hypoglycemia. The fact that more women than men have hypoglycemic episodes was attributed to gender, as it was shown that women have a lower counterregulatory threshold for hypoglycemia than men, especially in the elderly population.

Table 1. Risk Factors for Hypoglycemia in the ICU

Use of continuous venovenous hemofiltration with bicarbonate-based substitution fluid

Gastric residual removal during enteral nutrition without adjusting insulin administration

Lowering or stopping nutrition without adjusting insulin administration

Severe sepsis or septic shock

Simultaneous use of insulin and octreotide

Inotropic support

Mechanical ventilation

Tight glycemic control range

Repeated doses of subcutaneous insulin

History of diabetes mellitus

Renal failure

Liver failure

Medications associated with hypoglycemia: oral antidiabetic agents, β-blocking agents, quinine, aspirin (acetylsalicylic acid), trimethoprim-sulfamethoxazole, pentamidine, disopyramide

Medications associated with hyperglycemia: catecholamines, glucocorticoids

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ACUTE DIABETIC EMERGENCIES

Hyperglycemic emergencies of diabetes can be divided into diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS). The pathogenesis of both of these hyperglycemic disorders lies between complete or relative insulin deficiency and unopposed counterregulatory hormones, most importantly glucagon. Both conditions are characterized by hyperglycemia, which triggers osmotic diuresis and leads to severe dehydration and hyperosmolarity (**Table 2**). The actual level of hyperglycemia is less important than the cause or associated abnormalities of the elevated BG levels. The initiation of osmotic diuresis promotes loss of potassium, phosphate, magnesium, chloride, and sodium. Fluid depletion during DKA is estimated to be around 5 to 7 L, whereas this number is typically higher than 9 L during HHS in most adults. Significant volume depletion triggers a renin-angiotensin-aldosterone cascade, causing more potassium depletion. Before initiating treatment for either DKA or HHS, the clinician must measure the patient's potassium level; a potassium deficiency, if present, must be treated to avoid dangerous worsening of hypokalemia. Insulin treatment should be deferred until serum potassium is more than 3.5 mEq/L. In DKA, with the help of glucagon, the release of fatty acids results in ketone production, which in turn causes an anion gap metabolic acidosis via depleting buffer capacity. HHS differs from DKA with the absence of ketones, likely

secondary to the presence of scarce amounts of insulin, which prevents ketone production by blocking fatty acid oxidation. Worldwide, infection is the most common precipitating factor for both DKA and HHS, being responsible for half of the cases. Other predisposing conditions known to trigger DKA or HHS include cardiovascular events, trauma, surgery, pregnancy, substance abuse, and noncompliance with treatment.

Table 2. Distinguishing Features of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome

Diabetic Ketoacidosis	**Hyperosmolar Hyperglycemic Syndrome**
Patients with type 1 > type 2 diabetes mellitus	Patients with type 2 diabetes mellitus
Younger patients	Elderly patients
Symptoms develop within 24 hours of ketoacidosis	Symptoms develop over days to weeks
Abdominal pain and nausea	Prominent mental status changes
Blood glucose >250 mg/dL	Blood glucose >600 mg/dL
Presence of ketones, fruity breath	Osmolarity >320 mOsm/kg
Ketoacidosis, pH <7.3 (anion gap metabolic acidosis)	Absent or mild ketoacidosis

The syndrome of DKA consists of a triad of hyperglycemia, acidosis, and ketonemia. Diagnostic criteria are defined by the American Diabetes Association (ADA) as BG more than 250 mg/dL, pH less than 7.3, serum bicarbonate less than 18 mEq/L, anion gap more than 10, and presence of ketones in the serum. The majority of DKA cases occur in patients with type 1 DM; however, it is now clear that patients with type 2 DM, especially African Americans and other ethnic minorities, may suffer from this condition. The cause of this possible ethnic difference is unclear. The presentation of DKA, unlike HHS, usually occurs within 24 hours of ketoacidosis occurrence. Patients complain of polyuria, polydipsia, weight loss, vomiting, and, specifically for DKA, abdominal pain. Physical examinations of these patients reflect signs of hypovolemia. Fruity odor in the breath and Kussmaul respirations may be observed. Confusion can also be present in DKA, although it is more common with HHS.

Only about 1% of diabetes-related hospital admissions are attributed to HHS, but it has a higher mortality than DKA: up to 15% for HHS versus up to 2% for DKA. Higher mortality is likely due to underrecognition and more frequent presence of severe comorbidities. HHS can be diagnosed by the presence of hyperglycemia with BG more than 600 mg/dL and the presence of hyperosmolarity, in which serum osmolarity is usually 320 or higher. Serum bicarbonate level and pH are expected to be within normal limits. HHS tends to occur in the elderly population, with presenting symptoms that are very similar to those of DKA but that develop over several days to weeks. Altered mental status triggered by severe volume depletion is usually the reason patients are brought to a physician's attention.

All critically ill patients who present to ICUs with altered mental status, severe hypovolemia, hypotension, acid-base disturbances with severe electrolyte imbalance, and suspected association with myocardial infarction or infection should be screened for both DKA and HHS. Diagnosis can be made easily via a POCT device to determine BG levels and the presence of ketones, by venous and arterial blood gas analysis, and by a basic metabolic profile for calculation of serum osmolarity, electrolyte imbalances, and anion gap calculation. Electrolyte imbalances must be diligently managed during the care of both of these hyperglycemic emergencies. Total body potassium is severely depleted because of renal losses, which can be as high as 3 to 5 mEq/kg in DKA and 4 to 6 mEq/kg in HHS. Despite this, the initial potassium value might be within normal ranges because of extracellular potassium shifts under the influence of pH and osmolarity changes. Regardless, before initiation of insulin treatment for either hyperglycemic state, a normal potassium level should be established to avoid development of severe hypokalemia, and additional potassium repletion will likely be required during ongoing therapy. Sodium and chloride are also severely lost during osmotic diuresis. It is well described that hyperglycemia lowers the serum sodium concentration to maintain normal osmolarity. It has been recommended to correct for this by adding 1.6 mEq of sodium for every 100 mg of glucose over the 100-mg glucose level; however, for BG values higher than 400 mg/dL, a correction factor of 2.4 seems more accurate than 1.6. Depletions of phosphorus, calcium, and magnesium are usually masked by initial hemoconcentration, and they should be expected to become apparent as hypovolemia is corrected. Elevated hemoglobin and leukocytosis can also be present. Mild leukocytosis of 10,000 to 15,000/mm^3 can be attributed to stress and dehydration. White blood cell counts of 25,000 and higher should be handled as bacterial infections until proven otherwise.

MANAGEMENT OF HYPERGLYCEMIC EMERGENCIES

The treatment goals for both DKA and HHS are correction of hypovolemia, reestablishment of normoglycemia, correction of electrolyte imbalances, and treatment of predisposing factors. Patients with altered mental status, oliguria, severe hypokalemia, hypothermia, or other significant associated comorbidities such as cardiovascular incidents, recent surgery, infection, or stroke should be treated in ICUs during management of these complex disturbances. With suspected diagnosis (positive signs via bedside glucometry and urine dipstick) of DKA or HHS, treatment should be initiated promptly with fluid replacement, without waiting for further laboratory results. The rate of volume repletion depends on the patient's cardiovascular status as well as severity of clinical presentation. Metabolic disturbances should be corrected at a more conservative rate than volume replacement, since rapid correction can harm the patient. The end-point of therapy is resolution of hyperosmolarity (in HHS) and metabolic acidosis (in DKA) with correction of anion gap after proper management of hyperglycemia, hypovolemia, and associated metabolic imbalances.

Volume Repletion During Hyperglycemic Emergencies

The initial choice for fluid replacement should be 0.9% sodium chloride (ie, normal saline [NS]). One liter of NS should be initiated immediately with suspicion of DKA or HHS. After clinicians determine a calculated corrected serum sodium level, the choice of crystalloids can be altered. If corrected serum sodium is less than 135 mEq/L, replacement can be continued with NS. But if corrected serum sodium is more than 135 mEq/L, clinicians should consider changing to 0.45% sodium chloride; by the time the corrected sodium is in the high normal range, the patient should be receiving 0.45% sodium chloride. Fluid replacement should be monitored frequently and tailored individually for each patient. Typically, the recommendation is to give the first 2 L in the first 2 hours, the next 2 L in 2 to 6 hours, and an additional 2 L in the following 6 to 12 hours. This algorithm usually replaces 50% of the fluid deficit in the first 8 to 12 hours, and then the rest should be administered within the following 12 to 16 hours. Fluid administration may need to be more judicious in patients with renal or cardiac impairment, and these patients must be monitored carefully. Volume replacement alone decreases serum glucose concentration by up to 50 mg/dL by restoring renal perfusion and glycemic diuresis. It is imperative to check BG levels frequently to monitor the rate of correction. Dextrose should be added to replacement fluids when the BG level drops to 250 to 300 mg/dL.

Insulin Treatment

Insulin administration increases utilization of glucose in peripheral tissues and decreases hepatic gluconeogenesis by opposing counterregulatory hormones. Fluid administration should always be the first-line therapy, and insulin therapy should be started after initial fluids are given. A dose of 10 to 15 U of short-acting analog or regular insulin intravenously should be followed by a continuous insulin infusion of 0.1 U/kg/h to achieve a steady decrease in serum glucose of 50 to 75 mg/dL/h. It is imperative that potassium levels be aggressively monitored during this treatment as both fluid and insulin therapy cause rapid decreases in potassium levels and predispose the patient to dysrhythmias.

Although initial volume replacement reduces side effects of the counterregulatory hormones, insulin also helps by decreasing fatty acid production, decreasing ketonemia, and correcting acidosis. Initial serum potassium concentration should be measured before initiation of insulin therapy; insulin administration should be deferred until potassium levels are corrected, since insulin treatment can trigger life-threatening hypokalemia from extracellular to intracellular shift. The ADA recommends that patients whose initial potassium levels are between 3.3 and 5 mEq/L receive potassium at 10 to 15 mEq/L/h in their replacement fluids for at least 4 hours, presuming urine output is maintained.

Continuous low-dose IV insulin therapy (0.1 U/kg/h) continues to be a fundamental therapy for hyperglycemic states, since it allows for a steady decrease in BG along with volume replacement. Intramuscular or subcutaneous administration of short-acting or regular insulin should be avoided in early treatment since absorption might be affected by severe volume depletion in these hyperglycemic states. Continuous insulin therapy should be maintained until the anion gap is corrected, even after resolution of hyperosmolarity, since it may take longer to resolve than hyperglycemia in DKA states. Therefore, 5% dextrose should be added to replacement fluids to continue insulin infusion; ongoing recovery should be monitored via anion gap measurements.

Morbidity, Mortality, and Complications Associated With Hyperglycemic Emergencies

Among predisposing factors for DKA and HHS, myocardial infarction and infection contribute the most to mortality. Excluding the predisposing causes,

cerebral edema due to rapid correction of hyperosmolar states, refractory shock due to severe volume depletion, vascular thrombosis, and superimposed infections can significantly influence the outcome of patients during these diabetic emergencies. Electrolyte imbalances during treatment include hypoglycemia, hypokalemia, and hypophosphatemia, and all three can affect morbidity and mortality rates. Mismanaged hyponatremia can complicate treatment with seizures, altered mental status, or life-threatening cerebral edema. Acute respiratory distress syndrome can occur during management of these states. Although the pathogenesis of acute respiratory distress syndrome with DKA or HHS is not clear, it is believed to be caused by excessive volume replacement. Mucormycosis, a rare opportunistic fungal infection, can complicate recovery from DKA by either pulmonary or rhinocerebral mucormycosis. New onset of fever during the recovery of either hyperglycemic state mandates a thorough examination of sinuses and nasal turbinates, since prognosis of mucormycosis is very poor even with antifungal therapy and debridement.

SUMMARY

- Pathophysiological process of hyperglycemia in critically ill patients: Previously diagnosed diabetes, new-onset diabetes, and undiagnosed diabetes and SIH are the most common causes of hyperglycemia in the ICU. Mechanisms for the pathophysiological process include, but are not limited to, insulin resistance, absolute or relative insulin deficiency, impaired glucose metabolism, and effects of stress-induced hormones such as glucagon and corticosteroids as well as nutritional supplements.
- Recent consensus statements and guidelines: In 2015, the American Association of Clinical Endocrinologists, the American College of Endocrinologists, and the ADA continued to recommend that insulin therapy for persistent hyperglycemia in the ICU be initiated at a threshold BG level of 180 mg/dL or more. The 2012 SCCM guidelines recommend starting insulin therapy if BG is 150 mg/dL or more. Once insulin therapy is initiated, all of these guidelines recommend a target BG range of 140 to 180 mg/dL for the majority of critically ill patients. Intravenous insulin infusions are the preferred method of insulin administration for ICU patients.
- Risk factors for hypoglycemia in the ICU: Severe sepsis, shock requiring

vasoactive agent support, decreases of nutritional input without adjustments in insulin infusion, treatment with insulin, preexisting diabetes, mechanical ventilation, liver or renal failure, increased severity of illness, and continuous venovenous hemofiltration with bicarbonate-based substitution fluid are leading risk factors for hypoglycemia in the ICU.

- Diagnostic criteria for DKA: DKA is a triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia with diagnostic criteria defined by the ADA as BG greater than 250 mg/dL, pH less than 7.3, serum bicarbonate less than 18 mEq/L, anion gap more than 10, and ketone presence in the serum.

- The main differences between DKA and HHS are their treatment end-points: HHS can be diagnosed with BG more than 600 mg/dL and a serum osmolarity typically 320 mOsm/kg or greater. Serum bicarbonate level and pH are expected to be within normal limits. HHS tends to occur in the elderly population, with presenting symptoms that can be traced back over several days to weeks, unlike the early presentation of DKA. Treatment goals for both DKA and HHS include correction of hypovolemia, reestablishment of normoglycemia, correction of electrolyte imbalances, and treatment of predisposing factors. The end-point of therapy is resolution of hyperosmolarity in HHS and resolution of metabolic acidosis in DKA after proper management of hyperglycemia, hypovolemia, and associated metabolic derangements.

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CHAPTER 37

Pituitary, Adrenal, and Thyroid Diseases in the Critically Ill Patient

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Key words: critical illness–related corticosteroid insufficiency, sick euthyroid syndrome, thyroid storm

Exposure of the host to diverse noxious stimuli results in a stereotypical and coordinated response, referred to by Hans Selye as the "general adaption syndrome" (or stress response), which restores homeostasis and enhances survival. The stress response is mediated primarily by the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis results in increased secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus of the hypothalamus. CRH plays a pivotal integrative role in the response to stress; CRH stimulates the production of corticotropin by the anterior pituitary, causing the zona fasciculata of the adrenal cortex to produce more glucocorticoids (cortisol in humans). AVP is a weak corticotropin secretagogue and vasoactive peptide that acts synergistically with CRH to increase secretion of corticotropin. In addition, the HPA axis and immune system are closely integrated in multiple positive and negative feedback loops. In general, cortisol levels correlate with the severity of injury, Glasgow Coma Scale score, and Acute Physiology and Chronic Health Evaluation score. The increase in cortisol production results in multiple effects (metabolic, cardiovascular, and immune) aimed at restoring homeostasis during stress. Cortisol has potent anti-inflammatory actions including the reduction in number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils, at sites of inflammation. Cortisol is the most important inhibitor of the transcription of proinflammatory mediators (inhibits nuclear factor-κB and activator protein 1) by multiple mechanisms.

Dehydroepiandrosterone and dehydroepiandrosterone sulfate are the most abundant steroids secreted by the adrenal cortex and are under CRH control. Only dehydroepiandrosterone is considered biologically active, mediating its action mainly indirectly via downstream conversion to sex steroids. Dehydroepiandrosterone is a pleiotropic adrenal hormone with proimmune and proinflammatory effects, opposing the immunosuppressive effects of glucocorticoids. Dehydroepiandrosterone and dehydroepiandrosterone sulfate levels may be depressed in the acute phase of severe illness. The implications of these findings are unclear; however, a high ratio of cortisol to dehydroepiandrosterone has been suggested to be a poor prognostic marker in patients with severe sepsis.

HPA AXIS DYSFUNCTION: CRITICAL ILLNESS–RELATED CORTICOSTEROID INSUFFICIENCY

Increasing evidence shows that in many critically ill patients, activation of the HPA axis and the release of cortisol are impaired, consistent with adrenal insufficiency [AI]. The reported incidence of AI varies widely (0%-77%) depending on the population of patients studied and the diagnostic criteria used. However, the overall incidence of AI in critically ill patients approximates 10% to 20%, with an incidence as high as 60% in patients with septic shock. The major sequelae of AI in critically ill patients involve the systemic inflammatory response (excessive inflammation) and cardiovascular function (hypotension).

Until recently, investigations into the exaggerated proinflammatory response that characterizes patients with systemic inflammation focused on suppression of the HPA axis and “adrenal failure.” However, experimental and clinical data suggest that corticosteroid tissue resistance also plays an important role. This complex syndrome is referred to as *critical illness–related corticosteroid insufficiency* (CIRCI). CIRCI is defined as inadequate cellular corticosteroid activity for the severity of the patient’s illness. CIRCI manifests with insufficient corticosteroid-mediated downregulation of inflammatory transcription factors. The mechanisms leading to dysfunction of the HPA axis and tissue glucocorticoid resistance during critical illness are complex and poorly understood.

CIRCI is most common in patients with severe sepsis (septic shock). In addition, patients with liver disease have a high incidence of AI (hepatoadrenal syndrome). CIRCI should be considered in patients with pancreatitis. A subset of patients may experience structural damage to the adrenal gland from either hemorrhage or infarction, and this can result in long-term adrenal dysfunction.

Furthermore, a number of drugs are associated with adrenal failure (**Table 1**). However, most patients with AI (and CIRCI) develop reversible dysfunction of the HPA system; this is probably mediated by inflammatory mediators, may be self-perpetuating, and follows the same time course of the immune deregulation seen in patients with sepsis and systemic inflammatory response syndrome.

Table 1. Causes of Adrenal Insufficiency and Critical Illness–Related Corticosteroid Insufficiency

Reversible Dysfunction of Hypothalamic-Pituitary-Adrenal Axis	Primary AI	Glucocorticoid Tissue Resistance
Sepsis/systemic inflammatory response syndrome	Autoimmune adrenalitis	Sepsis
Pancreatitis	HIV infection Highly active antiretroviral therapy HIV	Systemic inflammatory response syndrome Acute respiratory distress syndrome Trauma Burns Pancreatitis Liver failure Post cardiac surgery HELLP syndrome
Drugs Corticosteroids (secondary AI) Ketoconazole (primary AI) Etomidate (primary AI) Megestrol acetate (secondary AI) Rifampin (increased cortisol metabolism) Phenytoin (increased cortisol metabolism) Metyrapone (primary AI) Mitotane (primary AI)	Cytomegalovirus	
	Metastatic carcinoma Lung Breast Kidney	
Hypothermia	Systemic fungal infection Histoplasmosis Cryptococcus Blastomycosis	
	Tuberculosis	
	Adrenal hemorrhage and infarction Disseminated intravascular coagulation Meningococcemia Anticoagulation Antiphospholipid syndrome Heparin-induced thrombocytopenia Trauma	

Abbreviations: AI, adrenal insufficiency; HELLP, hemolysis, elevated liver enzymes, low platelet count.

Diagnosis of Adrenal Insufficiency or CIRCI

No clinically useful tests are available to assess the cellular actions of cortisol;

thus, the accurate clinical diagnosis of CIRCI remains somewhat elusive. Furthermore, although the diagnosis of AI in the critically ill patient is fraught with difficulties, at this time this diagnosis is best made by (1) a random (stress) cortisol level less than 10 μg/dL or (2) a delta cortisol less than 9 μg/dL after a 250- μg corticotropin stimulation test. These diagnostic criteria have a high specificity (95%) but a low sensitivity (36%). Based on the results of the cosyntropin stimulation test, it may be useful to divide CIRCI into 2 subgroups: type I, characterized by a random (stress) cortisol less than 10 μg/dL, and type II, characterized by a random cortisol 10 μg/dL or greater with a delta cortisol less than 9 μg/dL. Patients with type II CIRCI have been reported to have high circulating levels of proinflammatory mediators, a significantly higher severity of illness (higher Simplified Acute Physiology Score), and a higher mortality than patients with type I CIRCI. The therapeutic implications of these subgroupings are unclear.

Which Patients Should We Treat With Steroids?

Patients with severe sepsis and septic shock are frequently treated with exogenous glucocorticoids. Large geographic variations are seen in the prescription of glucocorticoids for sepsis, but up to 50% of ICU patients receive such therapy. Despite more than 30 years of investigation and more than 20 meta-analyses, the use of glucocorticoids in patients with sepsis remains extremely controversial, with conflicting recommendations. The most important recent studies are the investigation by Annane et al (*JAMA.* 2002 Aug 21;288(7):862-71) and the Corticosteroid Therapy in Septic Shock (CORTICUS) study (*N Engl J Med.* 2008 Jan 10;358(2):111-24). Both of these studies have important limitations, in that 24% of patients received etomidate in the Annane study, whereas 19% received etomidate in the CORTICUS study (see subsequent discussion of etomidate). The benefit of glucocorticoids in the Annane study may have been largely restricted to those patients who received etomidate. Furthermore, only patients with “refractory septic shock” were enrolled in the Annane study, whereas an overwhelming selection bias resulted in only approximately 5% of eligible patients being enrolled into the CORTICUS study.

Furthermore, Volbeda et al (*Intensive Care Med.* 2015 Jul;41(7):1220-34) performed a systematic review of all randomized controlled trials studying the effect of corticosteroids in sepsis and septic shock. Their study included 35 trials (4,682 patients) and found no significant effect of steroids on mortality or other significant adverse events in patients receiving low- or high-dose steroids.

Nevertheless, other systematic reviews suggest that (1) treatment of septic shock with low-dose glucocorticoids for 7 days significantly reduces vasopressor dependency (corticotropin responders and nonresponders) and ICU length of stay; (2) short-course, high-dose corticosteroids are not beneficial; (3) glucocorticoids appear to be of no benefit in patients who are at a low risk of dying; and (4) although the outcome benefit of low-dose glucocorticoids in patients with septic shock remains controversial, such a strategy appears to be safe (no excess mortality, superinfections, or acute myopathy). The Surviving Sepsis Campaign 2012 guidelines recommend intravenous hydrocortisone (200 mg/d) if hemodynamic stability cannot be restored with fluids and vasopressors; therapy should be weaned once vasopressors are not needed.

The complications associated with the use of corticosteroids depend on the dose, the dosing strategy, and the duration of therapy. In the ICU, the most important complications include immune suppression with an increased risk of infections (typical and opportunistic), impaired wound healing, hyperglycemia, myopathy, hypokalemic metabolic acidosis, psychosis, and HPA axis and glucocorticoid receptor suppression. The effect of glucocorticoids on immune suppression is critically dose dependent. It is well known from experience with organ transplant that high-dose corticosteroids effectively abolish T-cell–mediated immune responsiveness and are very effective in preventing and treating graft rejection. However, although stress doses of corticosteroids downregulate (but do not suppress) systemic inflammation with decreased transcription of proinflammatory mediators, they maintain innate and Th1-cell immune responsiveness and prevent an overwhelming compensatory anti-inflammatory response. In fact, new cumulative evidence indicates that downregulation of life-threatening systemic inflammation with prolonged low- to moderate-dose glucocorticoid treatment improves innate immunity and provides an environment less favorable to the intracellular and extracellular growth of bacteria. At stress doses, corticosteroids have been shown to increase neutrophil activity, increase the homing of dendritic cells with preservation of monocyte function, preserve function of interleukin 12, and attenuate the overwhelming inflammatory response. In the ARDSNet study (*N Engl J Med.* 2006 Apr 20;354(16):1671-84) corticosteroid treatment was associated with a reduction in nosocomial pneumonia. This finding is supported by the Hydrocortisone Polytraumatise (HYPOLYTE) study (*JAMA.* 2011 Mar 23;305(12):1201-9), which randomized patients with multiple trauma to hydrocortisone or placebo. The major end point of this study, hospital-acquired pneumonia, was significantly reduced in the patients randomized to hydrocortisone (35.6% vs 51.3%, $P = 0.007$). Similarly,

although myopathy is common in patients treated with high-dose corticosteroids, this complication is uncommon with stress dose of corticosteroids.

In summary, the risk-benefit ratio of glucocorticoids should be determined in each patient. A course of low-dose hydrocortisone (200 mg/d) should be considered in vasopressor-dependent patients (dosage of norepinephrine or equivalent >0.1 µg/kg/min) within 12 hours of the onset of septic shock. Steroids should be stopped in patients whose vasopressor dependency has not improved with 2 days of glucocorticoids. Infection surveillance is critical in patients treated with corticosteroids.

Furthermore, the use of etomidate as an anesthetic induction agent in critically ill patients is controversial, as this agent inhibits the 11β-hydroxylase enzyme that converts 11β-deoxycortisol into cortisol in the adrenal gland. A single dose of etomidate has been demonstrated to inhibit cortisol production for up to 48 hours, prompting the suggestion of steroid supplementation during this period. In the Annane study (*JAMA.* 2002 Aug 21;288(7):862-71), 72 patients received etomidate within 3 hours prior to randomization, and of these 68 were nonresponders; in this group of nonresponders, the mortality was 54% in those treated with corticosteroids compared with 75% in those who received placebo. In the CORTICUS study, 96 patients received etomidate a median of 14.5 hours prior to randomization. In this study, etomidate was identified as an independent risk factor for death, with this risk being unaffected by treatment with glucocorticoids. These data suggest that critically ill patients who have received an intubating dose of etomidate should probably be treated (within 6 hours) with stress doses of hydrocortisone for 24 hours (200 mg on day 1, 100 mg on day 2).

A suggested treatment approach is outlined next. Corticosteroids should not be stopped abruptly; this will lead to a rebound of inflammatory mediators with an increased likelihood of hypotension, rebound inflammation, or both. A continuous infusion of glucocorticoid may be associated with better (smoother) glycemic control. Because blood glucose variability has been demonstrated to have prognostic implications, this may be the preferable method of dosing.

Treatment of Acute Adrenal Insufficiency or CIRCI

- Hydrocortisone 50 mg IV should be administered every 6 hours or as a 100-mg bolus and then a 10-mg/h continuous infusion. Continuous infusion is recommended whenever possible. Steroid therapy should be tapered once vasopressors are no longer required. A suggested tapering schedule is as

follows:

- Hydrocortisone 50 mg IV every 8 hours for 3 to 4 days.
- Hydrocortisone 50 mg IV or orally every 12 hours for 3 to 4 days.
- Reinstitution of full-dose hydrocortisone with recurrence of shock or worsening oxygenation.
- Fludrocortisone 50 μg orally (optional).
- Hydrocortisone and methylprednisolone are considered interchangeable.
- Dexamethasone should be avoided; it lacks mineralocorticoid activity. Dexamethasone has a long half-life and suppresses the HPA axis; it should not be used pending a corticotropin stimulation test.

Addison Disease

Occasionally patients with preexisting primary AI (Addison disease) will be admitted to the ICU. Adrenal crisis may be the presenting complaint, or it may be present as a comorbidity. The causes of primary AI are listed in **Table 1**. Patients with chronic AI usually present with a history of weakness, weight loss, anorexia, and lethargy, with some patients complaining of nausea, vomiting, abdominal pain, and diarrhea. Clinical signs include orthostatic hypotension and hyperpigmentation (primary AI). Laboratory testing may demonstrate hyponatremia, hyperkalemia, hypoglycemia, and a normocytic anemia. These patients require glucocorticoid replacement therapy titrated to the level of stress.

Waterhouse-Friderichsen Syndrome

In 1911, Waterhouse described a case of bilateral adrenal hemorrhage in a child dying of apparent sepsis, and he reviewed several published cases. In 1918, Friderichsen wrote a similar review and added 2 more cases to the literature. Sudden onset of adrenal hemorrhage in the setting of sepsis was termed *Waterhouse-Friderichsen syndrome*. Most cases are associated with *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. Cases of Waterhouse-Friderichsen syndrome due to *S pneumoniae* almost always occur in patients with severe reticuloendothelial dysfunction, especially hyposplenism or splenectomy. The pathophysiological process leading to adrenal hemorrhage is poorly understood. The leading theories postulate either exotoxin-mediated

vasculitis or coagulopathy in association with disseminated intravascular coagulation.

HYPOTHALAMIC-PITUITARY-THYROID AXIS DYSFUNCTION

Thyrotropin (TSH) is released from the anterior pituitary gland and stimulates the thyroid gland. Thyroxine (T4) is released into the circulation predominantly by the thyroid gland. Approximately 80% of the circulating triiodothyronine (T3) is produced in peripheral tissues by 5′-deiodination of free T4, whereas the remainder is secreted by the thyroid itself. Type 1 iodothyronine 5′-deiodinase (D1) is responsible for the deiodination of T4 and reverse T3 (rT3) at the 5′ position of the phenolic ring. Type 3 iodothyronine 5′-deiodinase (D3) removes iodide from the 5′-position of the tyrosyl ring, leading to inactivation of T4 and generation of rT3. T3 is the active hormone, whereas free T4 is considered the prohormone. The function of T3 is to maintain metabolic stability; this hormone affects the function of every organ system. Reverse T3 is thought to be hormonally inactive and possibly inhibitory on T3 activity at the cellular level and on D1.

Serum thyroid hormone levels undergo predictable changes in systemic nonthyroidal illness. The initial change in the hypothalamic-pituitary-thyroid axis during a mild illness is a decrease in T3 production caused by inhibition of the conversion of T4 to T3, with a reciprocal increase in rT3; this process is variously called *low T3 syndrome*, *nonthyroidal illness syndrome*, or *sick euthyroid syndrome* (SES). This decrease can occur very rapidly, and both the decrease in serum T3 and the increase in rT3 have been reported to correlate with severity of illness. T4-binding globulin levels are usually decreased, as is the total T4; however, free T4 is usually normal, as are the TSH levels. With severe disease and in patients with chronic illness, the free T4 (T4 syndrome) and TSH may decrease. The cause of SES is poorly understood; however, cytokines, most notably interleukin 1 and interleukin 6, may play a role by decreasing hepatic 5′-deiodinase type 1 expression. Derangement in hypothalamic and pituitary function may also contribute to the pathogenesis of SES. These changes in thyroid function are considered adaptive—an attempt to decrease catabolism and energy expenditure at a time of need. Whether this syndrome is maladaptive under certain circumstances is debatable. SES is observed in about 70% of hospitalized patients with diseases of various causes and is almost universal in critically ill patients. In a cohort of patients undergoing mechanical ventilation, the incidence of SES was reported to be

79%; patients with SES had a higher Simplified Acute Physiology Score II, duration of mechanical ventilation, and mortality. Leon-Sanz and coauthors (*Eur J Med Res.* 1997 Nov 28;2(11):477-82) studied the hypothalamic-pituitary-thyroid axis in 27 patients with septic shock. All patients had SES. However, survivors were characterized by a greater TSH response to TSH-releasing hormone (TRH), and only survivors demonstrated an increase in T3 over time (by day 5). SES is common following myocardial infarction and stroke, and rT3 levels are an independent predictor of mortality.

The role of thyroid hormone replacement in patients with SES is controversial. Brent and Hershman (*J Clin Endocrinol Metab.* 1986 Jul;63(1):1-8) randomized medical ICU patients with severe SES (low free T4) to receive T4 (1.5 μg/kg) daily for 2 weeks or placebo. In the treatment group, total T4 and free T4 concentrations increased significantly by day 3 and were normalized by day 5. A significant increase in T3 occurred in the control group on day 7 but was delayed until day 10 in the treatment group. Mortality was equivalent in the 2 groups (75% control vs 73% treatment). In a study of severely burned patients given 200 μg of T3 daily, no evidence of benefit from thyroid replacement was found. In a randomized controlled study of patients with acute renal failure, treatment with T4 (150 μg 4 times daily over 2 days) was associated with an increase in mortality compared with the control group (43% vs 13%). Van den Berghe et al (*J Clin Endocrinol Metab.* 1998 Feb;83(2):309-19) investigated the effects of a continuous infusion of TRH alone and in combination with growth hormone (GH)–releasing hormone and GH-releasing peptide 2. Twenty adult patients who remained critically ill for several weeks were studied. Reduced pulsatile secretions of TSH, GH, and prolactin were noted with low concentrations of T4, T3, and insulin growth factor 1 (IGF-1) in the untreated state. With TRH infusion alone, the thyroid axis could be reactivated, resulting in TSH secretion and increases in T4 and T3. Infusion of TRH in combination with GH secretagogues augmented the pulsatility of the TSH release and avoided an increase in rT3. These data suggest that in patients with SES, treatment with T4 or T3 alone may not be beneficial. The administration of TSH secretagogues seems to have a more physiological effect; however, additional studies are required before this therapy can be recommended. Although scant evidence is available to support treating SES, levothyroxine absorption may be impaired in critically ill patients (because of decreased gastric acidity), requiring dose escalation of T4 titrated to TSH levels in patients with preexisting hypothyroidism.

Thyroid Storm

Thyroid storm represents a rare, extreme manifestation of thyrotoxicosis. It is a life-threatening multisystem disease, with 20% to 30% of patients progressing to coma and death. Thyroid storm occurs in fewer than 10% of patients hospitalized for thyrotoxicosis. Patients with thyroid storm are best managed in an ICU. The most common underlying cause of thyroid storm is Graves disease. Graves disease is mediated by the TSH receptor antibodies that stimulate excess and uncontrolled thyroidal synthesis and secretion of thyroid hormones. It occurs most frequently in young women but can occur in either sex or any age group. Thyroid storm can also occur with a solitary toxic adenoma or toxic multinodular goiter. Precipitating factors associated with thyroid storm include infection, stress, diabetic ketoacidosis, labor, surgery, toxic ingestion of thyroid hormone, iodinated contrast studies, and medications (amiodarone), as well as cardiac and pulmonary diseases. The major presenting symptoms are anxiety, confusion, psychosis, palpitations, chest pain, dyspnea, diarrhea, weight loss, oligomenorrhea, and visual disturbances. On physical examination, the cardinal features include mental status changes, fever, and tachycardia out of proportion to the degree of fever. Patients have warm, moist skin and a widened pulse pressure. Atrial fibrillation and high-output cardiac failure are frequent findings. Features of Graves disease may be present, including a diffusely enlarged thyroid gland, ophthalmopathy, myopathy, and, in elderly patients, apathy. The differential diagnosis includes sepsis, neuroleptic malignant syndrome, malignant hypertension, heat stroke, and acute mania. A high index of suspicion is required to make the correct diagnosis.

Treatment often must be initiated before the results of thyroid function tests are available. Frequently, a poor correlation is found between the degree of elevation of T4 and T3 and the clinical manifestation of the thyroid storm. As only a small percentage of T4 and T3 are free and unbound (0.025% of T4 and 0.35% of T3) and because multiple conditions and drugs alter protein binding, free hormone concentrations are preferable in the diagnosis of thyrotoxicosis. Adrenocortical function is also affected because of acceleration of metabolism of endogenous cortisol, and reserves may be diminished. Leukocytosis, elevated liver function tests, hyperglycemia, and hypercalcemia may be present. The mainstay of therapy is aimed at reducing hormone synthesis, blocking hormone release, and preventing peripheral conversion of T4 to T3.

Propylthiouracil is the drug of first choice. Methimazole is considered an alternative first-line agent. Propylthiouracil and methimazole are thionamides

that prevent organification of iodine to tyrosine residues and the coupling of iodotyrosines. Propylthiouracil also inhibits peripheral conversion of T4 to T3. The adult loading dose of propylthiouracil is 600 to 1,200 mg, followed by 200 to 250 mg orally every 4 to 6 hours. Methimazole is dosed 20 to 25 mg orally every 6 hours. The most serious side effects of these drugs are agranulocytosis, hepatotoxicity, and a systemic vasculitis. Iodine blocks the release of T4 and T3 and is considered an adjunctive agent; Lugol’s solution is dosed 4 to 8 drops orally every 8 hours. Inhibition of thyroid gland synthesis of new thyroid hormone with a thionamide should be initiated before iodine therapy; this prevents the stimulation of new thyroid hormone synthesis that can occur if iodine is given initially. β-Adrenergic blocking agents are used for hyperadrenergic symptoms. β-Adrenergic blocking agents improve heart failure that is due to thyrotoxic tachycardia or myocardial depression. Propranolol is preferred because of its ability to decrease peripheral conversion of T4 to T3; the adult dose is 60 to 80 mg orally every 4 hours or 80 to 120 mg orally every 6 hours. Glucocorticoids are recommended if hypotension is present or underlying AI is suspected. Additional measures include the treatment of infections and other appreciating factors, aggressive hydration, and use of acetaminophen to treat hyperthermia (salicylates should be avoided because they increase free thyroid hormone levels). Plasmapheresis, charcoal hemoperfusion, and plasma exchange can be used to rapidly reduce levels of thyroid hormone in refractory cases.

Myxedema Coma

First described in 1879, myxedema coma is the most severe form of hypothyroidism. Myxedema coma usually occurs in elderly people during the winter months. It is a severe decompensated state of hypothyroidism which, if unrecognized, can carry a high mortality. The main distinguishing signs differentiating severe hypothyroidism from myxedema coma are hypothermia and hemodynamic instability with poor mentation leading to coma. The clinical severity cannot be assessed by the level of TSH. Mortality has improved over the last few decades from 60% to 25% given advances in supportive care. The most common precipitating factors include environmental hypothermia, stroke, sedative drugs, noncompliance with treatment of hypothyroidism, trauma, and infections.

Given that thyroid receptors are present in all organ systems, myxedema coma presents as a multisystem disease with the following major manifestations:

- Central nervous system: lethargy, decreased mentation, coma, seizures, delayed relaxation phase of deep-tendon reflexes.
- Metabolic: hypothermia, hyponatremia, hypoglycemia.
- Respiratory system: hypoxia, decreased respiratory drive with reduced muscle function leading to hypercarbia. May require mechanical ventilation in severe cases. Pleural effusion may lead to restriction of lung, and macroglossia causes obstruction of airway, which can worsen underlying sleep apnea.
- Cardiovascular system: bradycardia, diastolic hypertension, decreased pulse pressure, pericardial effusion with or without pericardial rub. Cardiomegaly, prolonged QT interval, dilated cardiomyopathy, and hypotension can occur in severe cases.
- Gastrointestinal system: constipation, decreased motility, gastric atony, nausea, fecal impaction. Ileus and megacolon can occur in severe cases.
- Renal system: decreased glomerular filtration rate, decreased free water clearance. Severe cases can present with acute renal failure.
- Endocrine system: excess vasopressin release leading to water retention. Associated AI.
- Integumentary system: coarse hair, dry skin, nonpitting edema.

Patients should be treated urgently once the diagnosis is suspected and before the results of thyroid function tests become available. Administration of the thyroid replacement hormone is lifesaving. Conversion of T4 to T3 in the peripheral tissues may be reduced in severe hypothyroidism due to decreased activity of the deiodinase enzyme. If T4 is used, an IV loading dose of 250 to 500 µg is recommended followed by 50 to 100 µg IV daily until the patient can take oral medications. T3 can be used with T4 or alone. The usual dose of T3 is 10 µg every 8 hours for the first 24 hours or until patient can take oral medications.

Cardiac complications are more common with T3 than T4. T3 should be used cautiously in patients with coronary artery disease. Additional supportive care includes fluids and vasopressor therapy, antibiotics for suspected or proven infection, hydrocortisone 50 mg every 6 hours IV (until AI is excluded), and correction of electrolytes. Hypothermia should be treated with passive rewarming, because active rewarming can worsen hypotension via

vasodilatation.

HYPOTHALAMIC-PITUITARY-GROWTH HORMONE DYSFUNCTION

Growth hormone is a polypeptide hormone with anabolic, immunomodulatory, and lipolytic properties. Its action is partly mediated via IGF-1, which is synthesized in the liver as well as the kidneys and pituitary gland. GH secretion is stimulated by GH-releasing hormone and inhibited by somatostatin. It is noteworthy that the pulsatile secretion of GH seems to be particularly important for its action. During the first hours or days after an acute insult, such as surgery, trauma, or infection, circulating GH levels become elevated and the normal GH profile, consisting of peaks alternating with virtually undetectable troughs, is altered; peak GH and interpulse concentrations are high and the GH pulse frequency is elevated. However, serum concentrations of IGF-1 and the GH-dependent binding protein, IGF binding protein 3, decrease. This reflects reduced GH receptor expression in peripheral tissues and results in acquired peripheral resistance to GH. It has been suggested that the proinflammatory mediators reduce GH receptor expression, which, in turn, through negative feedback inhibition, induces the abundant release of GH, exerting direct lipolytic, insulin antagonizing, and immune-stimulating actions, while the indirect IGF-1–mediated effects of GH are attenuated. In prolonged critical illness, lowered GH levels and a reduced pulsatile fraction have been found. As a result of this low pulsatility, levels of IGF-1 and IGF binding protein 3 are low. Low levels of IGF-1 are associated with muscle wasting.

To investigate the effect of administration of (high doses) of GH in critically ill patients, Takala et al (*N Engl J Med.* 1999 Sep 9;341(11):785-92) carried out 2 parallel, randomized controlled trials. A total of 532 patients who had been in the ICU for 5 to 7 days and who were expected to require intensive care for at least 10 days were enrolled. The in-hospital mortality rate was significantly higher in patients who received GH in both studies. Among the survivors, length of ICU stay was prolonged in the GH group. The study has been criticized for the very high dose of GH used, which may have been associated with insulin resistance and hyperglycemia, may have aggravated concealed hypoadrenalism and hypothyroidism, and may have promoted apoptosis in compromised tissue. Furthermore, it does not appear logical to administer high doses of GH to patients with prolonged critical illness who have normal to moderately decreased GH. Attempts to restore GH pulsatility with GH secretagogues may be more physiologically sound.

SUMMARY

The hypothalamic-pituitary peripheral-hormone axes are uniformly dysregulated in critical illness. The dysregulation of these axes is related to the severity of illness and is a dynamic process. Alterations observed in acute illness include increased serum GH and cortisol levels, blunted GH pulsatility, insulin resistance, hyperglycemia, and the low T3 syndrome. In prolonged critical illness, cortisol levels decrease compared with the acute phase, with a decrease in the levels of GH, TSH, and thyroid hormone. The management of these deregulated hormonal axes is controversial, with limited data supporting an improvement in outcome with hormonal replacement therapy.

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CHAPTER 38

Nutritional Therapies in Critically Ill Patients

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Key words: enteral nutrition, parenteral nutrition, immune-modulating nutrition, antioxidants

Historically, nutritional support of critically ill patients was aimed simply at preserving tissue mass and decreasing use of endogenous nutrient stores. However, recently this has evolved to be recognized as *nutritional therapy*, with goals that include decreasing catabolism and metabolic responses to stress, modulating immune responses, preventing oxidative damage at the cellular level, and maintaining and improving organ function. Major goals include decreasing infection, improving wound healing, maintaining the gastrointestinal (GI) barrier, decreasing complications and time of mechanical ventilation, and decreasing ICU and hospital stays and hospital costs.

Outcome after injury is related to adequate metabolic and hemodynamic resuscitation of critically ill patients. Roles of optimal delivery and timing, techniques of early feeding, comparisons of parenteral nutrition (PN) and enteral nutrition (EN), complications of nutritional therapies, nutrition for specific diseases, and a recommendation for an approach to feeding are covered in this chapter. Recently revised guidelines from the Society of Critical Care Medicine (SCCM) and American Society of Parenteral and Enteral Nutrition (ASPEN) provide an extensive review of key issues related to critical care nutrition, and the reader is referred to them for more details and references.

NUTRITIONAL ASSESSMENT

Traditional nutritional assessment begins by obtaining the patient's history from information in hospital records, from family members, or from the patient. Recent weight loss, anorexia, surgical history, activity levels, nausea and

vomiting, and diarrhea are important symptoms to elicit from the history.

Malnutrition is challenging to define in critically ill patients. In contrast, nutritional risk is easily defined and can be determined with evaluation of baseline nutritional status and assessment of disease severity. Hospitalized patients are required to have an initial nutritional screen within 48 hours of admission. But ICU patients at higher nutritional risk require a full nutritional assessment. Of tools available, only the Nutritional Risk Screening (NRS 2002) and the NUTrition Risk in the Critically ill (NUTRIC) score determine both nutritional risk and disease severity. Patients considered at risk have a NRS 2002 score less than 3, whereas those at high risk have a score of 5 or higher. Similarly, high risk is indicated by a NUTRIC score of 5 or higher (≥6 if interleukin 6 [IL-6] is included). Several studies have reported that patients at high nutritional risk are more likely to benefit from early EN with better outcomes than are patients at low nutritional risk.

Actual weights of critically ill patients may be of limited value because of water retention, and therefore weights may not correlate with nutritional status. Ideal body weights (IBWs) are typically more useful and are a practical estimate of lean body weight. A patient's IBW can be obtained from published actuarial tables and from nomograms based on height and body build characteristics or can be estimated by the following:

- Adult males: 106 lb for the first 5 ft of height and about 6 lb for each additional inch.
- Adult females: 100 lb for the first 5 ft and about 5 lb for each additional inch.
- Individuals older than 50 years are allowed an additional 10% of the calculated weights.

The ratio of actual body weight to IBW for a given gender, height, and age may establish the degree to which the patient is underweight and may reflect the degree of malnutrition: mild (80%-90%), moderate (70%-79%), and severe (<70%). Anthropometric measurements such as skinfold thickness and mid-arm muscle circumference are rarely useful in critically ill patients. Skinfold thickness (triceps or subscapular) measurements are a means of estimating body fat but are unreliable in the presence of fluid retention. Mid-arm muscle circumference is used to estimate body protein stores but is also unreliable in the

presence of fluid retention.

For some clinical situations, such as pharmacological volumes of distribution and drug dosing considerations, an adjusted body weight may be a better weight estimate to use. Adjusted body weight is typically calculated as follows:

$$\text{Adjusted Body Weight} = [\text{Adjustment Factor} \times (\text{Actual Weight} - \text{IBW})] - \text{IBW},$$

where the adjustment factor ranges from 0.2 to 0.5, and 0.25 is most commonly used for nutritional assessment purposes.

Laboratory tests used in nutritional assessment are not validated in critical care, and current guidelines suggest that these tests not be used as indicators of nutritional assessment or adequacy. Traditionally, measurements of visceral protein levels produced by the liver (ie, albumin, transferrin, prealbumin, and retinol-binding protein) were used to monitor responses to nutritional therapy. In critically ill patients, the traditional serum protein markers are affected by the acute phase response and so do not reflect nutritional status. Other markers such as C-reactive protein, calcitonin, IL-1, IL-6, and tumor necrosis factor should not be used as they are still under investigation.

Nitrogen balance studies may be helpful in assessing adequacy of nutritional protein intake. Nitrogen excretion amounts are best determined from 12- to 24-hour urine collections and measurements of total urinary nitrogen (more accurate than total urea nitrogen). These measurements may be unreliable in patients with renal failure or if urine is not correctly collected by staff. Nitrogen balance is calculated as nitrogen intake minus nitrogen lost (in urine, through the skin and stool, or from fistulas, wounds, or dialysates). Common estimates for normal nonurinary nitrogen excretion are 2 g/d each for skin and stool losses, but losses are difficult to estimate for patients with severe wounds and protein-losing enteropathies. Indeed, negative nitrogen balance is not necessarily detrimental over the short term (ie, 1-2 weeks). Some patients, for example, those with spinal cord injury or those receiving steroid therapy, will have high muscle protein turnover and increased nitrogen excretion. The belief is that a positive nitrogen balance of several grams per day is advantageous, but a simple improvement in sequential nitrogen balance studies can suggest that nutritional support is adequate. Still, nitrogen balance may improve as catabolism decreases despite inadequate nutritional support. In the care of dynamic patients, nitrogen balance studies can be difficult to interpret and may have limited value to the

clinical team.

Ultrasound is gaining attention as a tool to measure muscle mass and to follow changes in tissue mass in ICU patients. A computed tomography (CT) scan provides quantification of the skeletal muscle and adipose tissue, but CT is a costly way to measure muscle mass and usually is not used for this purpose alone. Reliability and validity of ultrasound and CT scans as nutritional assessments are not yet defined. Functional tests of nutritional status are traditionally used when feasible. Skin tests of immune function (ie, delayed cutaneous hypersensitivity) are frequently affected by critical illness, which limits their usefulness since many critically ill patients are anergic. Muscle strength assessment of grip or respiratory muscle function correlates with nutritional status but has limited utility in the ICU patient.

TIMING OF INSTITUTION OF NUTRITIONAL SUPPORT

Optimal timing of nutritional support cannot be determined by nutritional assessment indices, since many are altered by critical illness. Therefore, timing must be a clinical decision, but optimal timing remains controversial. Some patients tolerate short periods of starvation by using endogenous stores to support body functions. Well-nourished subjects (nonstressed) have survived without food for 6 weeks (ingesting only water). However, hypermetabolic and hypercatabolic critically ill patients can probably tolerate only a few weeks of starvation before death, and shorter periods of starvation are expected to contribute to organ dysfunction. Clearly, there appears to be no benefit of total starvation.

Data suggest that outcomes can be improved with early and optimal nutritional therapy. Extensive reviews of benefits of early nutritional support are found in guidelines published jointly by SCCM and ASPEN in 2016 as well as other international guideline groups. Briefly, early EN support blunts the hypercatabolic and hypermetabolic response to injury. In numerous studies, patients randomized to receive early versus delayed feeding had decreased infection rates, fewer complications, and shorter lengths of stay in the hospital. Animal studies in injury models report improvements in wound healing, renal function, hepatic function, and even mortality with early enteral feeding.

NUTRIENT REQUIREMENTS (QUANTITY)

Energy

Energy needs are met by the caloric content of the major nutrients (lipids provide 9 kcal/g, carbohydrates 4 kcal/g, and proteins 4 kcal/g). Studies show that most critically ill patients expend 25 to 35 kcal/kg/d. One can measure energy expenditure with indirect calorimetry or can estimate resting metabolic expenditure (RME) using the Harris-Benedict equation:

$$\text{Men: RME (kcal/d)} = 66 + (13.7 \times W) + (5 \times H) - (6.8 \times A)$$

$$\text{Women: RME (kcal/d)} = 665 + (9.6 \times W) + (1.7 \times H) - (4.7 \times A),$$

where W = weight in kilograms, H = height in centimeters, and A = age in years.

Historically, some have recommended adjusting RME by multiplying by a correction factor based on stress factors for burn injury, sepsis, or activity levels; however, correction factors frequently overestimate energy needs and are currently not recommended.

Indirect calorimetry, when available, is recommended to determine energy requirements unless it is likely to be inaccurate. Indirect calorimetry is commonly referred to as a *metabolic cart study* and is based on laws of thermodynamics: The use of energy involves the consumption of oxygen (ie, $\dot{V}O_2$) and the production of CO_2 (ie, $\dot{V}CO_2$), nitrogenous wastes, and water. When matter is converted to heat by the body, measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ indirectly reflects the metabolic energy expenditure. Typical studies measure $\dot{V}O_2$ and $\dot{V}CO_2$ for 15 to 30 minutes and then estimate energy expenditure and respiratory quotient (RQ), extrapolated to 24 hours. These studies should be performed while the patient is resting, that is, not during baths, respiratory treatments, physical therapy sessions, or other events that will increase stress and energy expenditure. Because of the short test period and extrapolation of data to a 24-hour estimate, large errors can occur, so clinical judgment plays a key role in interpretation of the results. Following measurements over time may allow clinicians to recognize changes in the metabolic rate and tailor nutritional support to meet an individual's needs. Several problems are associated with indirect calorimetry studies: Results can be inaccurate when the inspired oxygen fraction is greater than 0.40, any leak in the system can introduce error (eg, endotracheal tube cuff leak), and the test is labor-intensive because a steady state

is needed for accurate measurements (this can take an extended period of time to obtain in a critically ill patient).

Indirect calorimetry can provide an estimate of the RQ, which reflects whole-body substrate utilization.

The relationships between various fuels and their RQ are as follows:

- Carbohydrate: 1.0
- Fat: 0.70
- Protein: 0.80

The RQ can range between 0.70 and 1.2. Provision of excess carbohydrate calories results in net fat synthesis and leads to high CO_2 production (eg, RQ > 1.0), which should be avoided. The most obvious related problem is that excessive CO_2 production requires more ventilation for CO_2 elimination. This may increase the work of breathing in tenuous patients and can delay liberation from mechanical ventilation.

In the absence of indirect calorimetry, current recommendations are to initially administer 25 to 30 kcal/kg/d ∼20% protein, ∼30% lipids, ∼50% carbohydrates, which are percentages of total daily calories. Patients with obesity, organ failure, or some specific disease states may have increased or decreased needs and should be considered individually. Overfeeding (with either enteral or parenteral nutrients) is associated with more adverse side effects than is slightly underfeeding during most critical illnesses.

Protein

Most critically ill patients need 1.2 to 2.5 g of protein per kilogram of body weight per day. Protein requirements are often highest in patients with severe trauma, burns, and protein-losing enteropathies (**Table 1**).

Table 1. Macronutrient Nutritional Requirements of the Adult

Nutrient	% of Total Calories	Quantity of Nutrients	Example for 70-kg (154-lb) Patient
Total calories		25 kcal/kg/d	1,750 kcal/d
Protein, amino acids	15-25	1.2-2.0 g/kg/d	95 g/d (380 kcal/d) (based on 1.35 g/kg/d)

Carbohydrates	30-65	50% of calories (average patient)	220 g/d (880 kcal/d)
Fats	15-30	30% of calories (average patient)	55 g/d (495 kcal/d)

Water

Needs for water vary greatly between patients, primarily because of differences in insensible losses, GI losses, and urine losses. It is reasonable to initially estimate water needs as 1 mL of water per kilocalorie of energy expended in adults.

Vitamins

Vitamins A, D, E, and K are fat soluble. The water-soluble vitamins are ascorbic acid (C), thiamine (B_1), riboflavin (B_2), niacin, folate, pyridoxine (B_6), B_{12}, pantothenic acid, and biotin. Published recommended daily intakes (RDIs) are based on oral intake in healthy individuals. Vitamin needs for critically ill patients have not been determined. Commercial enteral formulas generally supply the RDI (or more) of vitamins if patients are given sufficient quantities of formula to meet their caloric needs. An adult parenteral vitamin formulation was approved by the US Food and Drug Administration (FDA) in 1979 and is available for addition to PN solutions; this should be added just before administration since degradation can occur. Recent drug shortages have included this IV vitamin preparation. When shortages occur, patients receiving PN more than a week are at greatest risk of deficiencies, and available vitamins should be rationed to these patients if necessary (**Table 2**).

Table 2. Micronutrient Nutritional Requirements of the Adult

Micronutrient	Enteral Nutrition	Parenteral Nutrition	Example for PN for a 70-kg (154-lb) Patient
Minerals			
Sodium	60-140 mmol/d	60-120 mmol/d	80 mmol/d
Potassium	50-140 mmol/d	50-120 mmol/d	50 mmol/d
Magnesium	8-15 mmol/d	8-12 mmol/d	10 mmol/d

Phosphorous	25 mmol/d	14-16 mmol/d	15 mmol/d
Calcium	20 mmol/d	7-10 mmol/d	10 mmol/d
Trace elements			
Iron	10 mg/d	1-2 mg/d	None
Zinc	15 mg/d	2-5 mg/d	5 mg/d
Copper	2-3 mg/d	0.5-1.5 mg/d	1 mg/d
Chromium	50-200 μg/d	10-20 μg/d	10 μg/d
Selenium	50-200 μg/d	80-150 mg/d	100 μg/d
Iodine	150 μg/d	120 μg/d	120 μg/d
Manganese	2.5-5.0 mg/d	0.2-0.8 mg/d	0.5 mg/d
Vitamins[a]			
Vitamin A	RDA = 4,000-5,000 IU/d	ND	3,300 IU/d
Vitamin D	RDA = 200-400 IU/d	ND	200 IU/d
Vitamin E	RDA = 12-15 IU/d	ND	10 IU/d
Vitamin K	RDA = 60-80 mg/d	ND	10 mg/wk[b]
Thiamine	RDA = 1.1-1.4 mg/d	ND	6 mg/d
Riboflavin	RDA = 1.2-1.7 mg/d	ND	5 mg/d
Niacin	RDA = 13-19 mg/d	ND	40 mg/d
Pantothenic acid	4-7 mg/d[c]	ND	15 mg/d
Pyridoxine	RDA = 1.6-2.0 mg/d	ND	4 mg/d
Folic acid	RDA = 0.4 mg/d	ND	0.4 mg/d
Vitamin B_{12}	RDA = 3 mg/d	ND	5 μg/d

Vitamin C	RDA = 40 mg/d	ND	100 mg/d
Biotin	RDA = 30-100 μg/d	ND	60 μg/d

Abbreviations: ND, not defined; PN, parenteral nutrition; RDA, recommended daily allowance.

[a]Enteral requirements should always exceed parenteral requirements; most recommend supplying 1-3 times the RDA of each vitamin to patients with critical illness (requirements are probably increased by stress, infection, disease). However, the exact requirements are not known.

[b]Consider withholding if warranted with anticoagulation.

[c]RDA not established.

Minerals (Sodium, Potassium, Calcium, Phosphate, Magnesium)

Minerals are present in sufficient quantities in enteral products (special formulas limit electrolytes for renal failure); however, they must be supplemented in PN (**Table 2**).

Trace Elements (Iron, Copper, Iodine, Zinc, Selenium, Chromium, Cobalt, Manganese)

Needs for trace elements in critically ill patients have not been determined (**Table 2**). Sufficient quantities are thought to be present in enteral products, but they must be supplemented in PN (all except iron can be added to solution). Deficiency states have been reported in patients receiving long-term PN (eg, copper, chromium). Specifics are best managed by specially trained nutritional support teams.

COMPARISON OF ENTERAL VERSUS PARENTERAL NUTRITION

In most cases EN is preferred over PN. Numerous randomized clinical trials involving a variety of critically ill patient populations have found benefits of EN over PN. Few studies have reported a mortality difference, and the most consistent benefit by EN is a decrease in infectious morbidity and ICU length of stay. EN is required for optimal gut function (ie, maintenance of gut barrier, gut-associated lymphoid tissue, immunoglobulin A secretion, mucin layer). PN is associated with immunosuppression (thought to be related to IV lipids available in the United States, which are high in *w*-6 long-chain fatty acids) and increased infection rates (compared with EN) in patients following trauma, burns, surgery, and cancer chemotherapy and radiotherapy. Extensive reviews of EN versus PN studies are found elsewhere. Historically, PN was used in patients with

inflammatory bowel disease or pancreatitis, but current data demonstrate that EN is preferred for both. Differences in outcome between EN and PN may diminish in the future with improvements based on protocolized management, glycemic control, and new lipid emulsions.

In patients at low nutritional risk (eg, NRS 2002 score ≤3 or NUTRIC score ≤5), exclusive PN can be withheld during the first 7 days after ICU admission if the patient cannot maintain volitional oral intake or can tolerate EN. Several meta-analyses suggest that delaying initiation of PN in low-risk patients is associated with better outcomes than using early PN. However, in patients with worse severity of illness or nutritional status, this is reversed, and if EN is not feasible in patients with high nutritional risk (eg, NRS 2002 score >5 or NUTRIC score >5), PN should be initiated soon after ICU admission. For patients who tolerate partial EN and are unable to meet more than 60% of needs enterally, supplemental PN should be considered after 7 to 10 days. Evidence suggests that it may be detrimental to use supplemental PN earlier in patients who are tolerating some EN. PN may be beneficial in specific populations, including those with short-gut syndromes, some types of GI fistulas, adynamic small bowel, or chylothorax. Recent SCCM-ASPEN critical care nutritional guidelines recommend that for most patients (ie, specifically those who are not at high nutritional risk on admission), PN should be deferred in the first days while EN is initiated, and PN use should be limited as described above. Of note, EN is less expensive than PN. **Table 3** compares the nutrient sources available in both EN and PN in the United States.

Table 3. Comparison of Nutrients in Enteral Versus Parenteral Nutrition

Nutrient	Enteral	Parenteral
Nitrogen source	Intact proteins, peptides, or amino acids	Amino acids[a]
Carbohydrate	Simple sugars or complex carbohydrates (ie, starch and fiber)	Simple sugar (dextrose)
Lipids	Long- and medium-chain triglycerides or long-chain fatty acids (*w*-3 or *w*-6)	Intravenous lipids[b]: 50%-65% linoleic acid (*w*-6) and 5%-10% linolenic acid (*w*-3)
Vitamins	Present	Can be added
Minerals and trace elements	Present	Can be added

[a]Lacks some conditionally essential amino acids (ie, glutamine and cysteine).

[b]Other IV lipid mixtures available in some countries but not in the United States.

ENTERAL NUTRITION SPECIFICS

In most cases, EN is the preferred route of nutritional therapy in both pediatric and adult patients. Delivery of EN can be achieved by several routes: oral, gastric tube (ie, nasogastric, gastric), or small bowel feeding tube (ie, nasoduodenal, gastroduodenal, jejunal). The optimal route of administration varies per individual patient. For most ICU patients, gastric feeds are technically easier and are likely to decrease time of initiation of EN. If a patient has high aspiration risk or has shown intolerance to gastric feeds, small bowel feeds are preferred. Studies have reported contradictory results as to risks of pneumonia with gastric versus small bowel feeds; however, aggregated data showed reduced risk of pneumonia with small bowel feeds, which are also associated with earlier delivery of nutritional targets enterally. Small bowel feeding may be preferred in mechanically ventilated patients who have frequent trips to operating rooms. Some ICUs have a protocol that allows small bowel feeds to continue in intubated patients until the patient leaves the ICU for the operating room; this diminishes nutritional deficits that otherwise develop following cumulative hours without feeds due to unexpected delays in scheduling of operative procedures and frequent nutritional holds. In a study of burn patients, small bowel feeds in patients who were already intubated (ie, mechanically ventilated patients) were safe without common preoperative nutrition holds and with continued intraoperative enteral feeding.

Major complications encountered with administration of EN are as follows:

- Aspiration (pneumonia, chemical pneumonitis, acute lung injury, or acute respiratory distress syndrome [ARDS])
- Metabolic derangements (electrolyte disturbances, hyperglycemia)—less common than with PN
- Diarrhea
- Misplaced feeding tubes (pneumothorax, empyema, bowel perforation)
- Overfeeding

RECOMMENDATIONS FOR USE OF PARENTERAL NUTRITION

Simply stated, PN should be used only when EN is not possible. Failure of the stomach to empty is not an indication for PN but rather for a small bowel feeding tube. Most patients with diarrhea can be managed with EN. Overall, PN management is best performed by specially trained nutritional support teams. Initial PN orders may be based on recommendations in **Tables 1** and **2**. PN can be delivered via peripheral vein but is more commonly administered in a concentrated preparation by central vein. After PN is initiated, EN should be considered daily and started as soon as deemed safe. As tolerance of EN improves, the amount of PN energy should be reduced and finally discontinued when the patient is receiving more than 60% of target energy requirements from EN. Conversely, the optimal time to start supplemental PN in a patient who continues to tolerate only hypocaloric EN is not clear and should likely be after 7 to 10 days. Several studies have reported detrimental effects and lack of improved outcomes when supplemental PN was initiated in the first several days of EN.

Major complications associated with PN administration are as follows:

- Central line placement complications (pneumothorax, hemothorax, carotid artery perforation)
- Metabolic derangements (hyperglycemia, electrolyte disturbances)
- Immune suppression
- Increased infection rates (catheter-related sepsis, pneumonia, abscesses)
- Liver dysfunction (fatty infiltration, cholestasis, liver failure)
- Gut atrophy (diarrhea, bacterial translocation)
- Venous thrombosis
- Overfeeding

In addition, PN lacks some conditionally essential amino acids that are not stable in solution (ie, glutamine, cysteine).

The glucose to fat ratio usually ranges from 60:40 to 40:60 (ratio of calories from each source). Large amounts of glucose (>60% of calories) can have the following undesirable effects:

- Increase energy expenditure
- Increase CO_2 production and increase pulmonary workload (may delay ventilator weaning)
- Produce liver steatosis
- Lead to immune compromise

ROLE OF SPECIFIC NUTRIENTS USED IN ENTERAL NUTRITION

Nitrogen Sources

Evidence suggests that peptides generated from the diet have specific physiological activities. Nitrogen is best delivered as intact protein; however, hydrolyzed protein or peptides may provide benefit when digestion is impaired. Essential amino acid formulas should not be used because they have been associated with worse outcomes when compared with either intact protein or peptide-based formulations.

Some typically nonessential amino acids become essential during critical illness, and these are called *conditionally essential amino acids* (eg, glutamine, cysteine, arginine, and taurine). Separate supplementation of these conditionally essential amino acids has not been shown to consistently improve outcomes even though some amino acids appear to have specific physiological roles:

- Glutamine is a fuel for the GI tract and immune system.
- Arginine is required for optimum wound healing and is important in immune function.
- Cysteine is needed for synthesis of glutathione.
- Glutamine and cysteine are not stable (or present) in PN solutions in the United States; IV glutamine dipeptides are available in some parts of the world for use in PN.

Lipids

Linoleic acid is an essential fatty acid that should make up 7% to 12% of total caloric intake for humans. It is an *w*-6 polyunsaturated, long-chain fatty acid (a

type of fatty acid that has been shown to be immunosuppressive) and is a precursor to membrane arachidonic acid. The lipids used in IV formulations marketed in the United States are primarily *w*-6 fatty acids. The *w*-3 polyunsaturated fatty acids are found in fish oils and linolenic acid (an essential fatty acid). They decrease production of dienoic prostaglandins (ie, PGE2), tumor necrosis factor, IL-1, and other proinflammatory cytokines. The medium-chain triglycerides are water soluble and are a good energy source. Medium-chain triglycerides enter the circulation via the GI tract. Short-chain fatty acids (eg, butyric and propionic acid) are a major fuel for the gut (especially the colon) and are derived from metabolizable fibers such as guar and pectin. Some enteral formulas were designed as high-fat formulas and are marketed for decreasing the RQ. However, if a patient is not overfed, these formulas have little effect on CO_2 production and are not recommended. A problem with these formulas is that they are associated with poor GI tolerance (bloating, diarrhea).

Carbohydrates

Starches and sugars are good energy sources. Fiber has several benefits. Metabolizable fiber is converted to short-chain fatty acids in the colon by bacteria, and data suggest that these fatty acids are beneficial to colonic health. Other fiber sources that are insoluble add bulk, which increases stool mass, softens stool, adds body to stool, and provides some stimulation of gut mass.

Antioxidants

A number of antioxidants are likely to benefit critically ill patients. Glutamine and cysteine can be rate-limiting substrates for synthesis of glutathione, which is believed to be the body’s major antioxidant. Based on current data, glutamine supplementation is not recommended as a routine enteral or parenteral supplement. Vitamins C and E are antioxidants as well and are likely needed in higher quantity during critical illness. Selenium has been reported to be deficient in some critically ill patients, and continuous infusion of selenium improved survival in one randomized trial of patients with severe sepsis. Numerous trials have demonstrated that antioxidant and trace element supplementation was associated with a significant reduction in overall mortality. But rates of infection, ICU or hospital length of stay, and duration of mechanical ventilation were not significantly different with or without antioxidant and trace element supplementation versus placebo. Dosage, route of administration, and frequency are not established, and renal function should be considered prior to

supplementation of trace elements and vitamins.

Nucleic Acids

Dietary nucleic acids (eg, ribonucleic acid) may be important for immune function and are added to some specialty formulations.

GASTROINTESTINAL FUNCTION DURING CRITICAL ILLNESS

Oral nutrition remains the best form of nutritional support; however, many critically ill patients cannot be fed by mouth. Mental status may preclude volitional intake. Decreased motility of the stomach and colon is common in critically ill patients and typically lasts 5 to 7 days (longer if a patient remains critically ill). Gastroparesis occurs but is not well assessed or monitored by measuring gastric residuals. Controversies surround the gastric residual volume that limits safety of gastric feeds. McClave and colleagues (2005) reported safety with residual volumes as high as 500 mL, and other studies confirm lack of efficacy of the historical practice of monitoring gastric residuals as a sign of tolerance of EN. Many critical care teams still monitor gastric residual volumes as a method of decreasing aspiration risk, but this is no longer recommended as it is more likely to limit delivery of nutrients than to add safety. Aspiration is one of the most dreaded complications of EN, so it is reasonable to consider small bowel delivery of enteral feeds in patients with high risk of aspiration. Besides small bowel feeding, an option for patients with gastroparesis is to administer a promotility agent such as erythromycin or metoclopramide. If promotility agents are used, a trial of stopping the agent should be considered after a few days of successful feeding at goal rate, as these agents may be needed only a few days. In critically ill patients, motility and nutrient absorptive capability of the small bowel are usually at least partially preserved even after severe trauma, burns, or major surgery. Bowel sounds are a poor index of small bowel motility and should not be used to decide whether EN should be attempted. Use of EN feeding protocols is associated with better delivery of nutritional support, and these protocols are recommended.

Recommended Approach to Enteral Feeding

A. EN support should be initiated within 12 to 48 hours of admission to ICU.

B. The gastric route is the second choice (oral is first choice) and should be

tried in most patients before a small bowel tube is placed.

C. Patients at high risk for aspiration or known gastric paresis should be fed with a small bowel tube.

D. Feeding formulas should not be diluted.

E. The head of the bed should be elevated 30° or more to decrease risk of aspiration.

F. In adults, feeding may be started at 25 to 30 mL/h and increased by 10 to 25 mL/h every 1 to 4 hours as tolerated by signs of tolerance until the caloric goal (25 kcal/kg/d) is reached.

G. Protein goals can be achieved by using a formula with a high protein-calorie ratio or by administering protein to the patient separately.

H. Feeds (for adults) can be increased at a slower rate (ie, ∼10 mL/h every 6-12 hours) for patients expected to have more intolerance, but often this is not necessary when feeds are started early.

I. Promotility agents such as metoclopramide or erythromycin may be added if gastric emptying is problematic; alternatively, small bowel tubes can be placed for feeds.

J. The goal rate of infusion should be met by the third day of nutritional therapy (frequently earlier).

K. Formula osmolality should be 300 to 600 mOsm/kg H_2O, and this osmolality rarely causes intolerance or diarrhea.

GENERAL CONCERNS REGARDING OVERFEEDING

Potential complications from overfeeding have led to recommendations of lower total daily caloric intakes (ie, initial goal of 25 kcal/kg/d) in adult critically ill patients than historically used. Indirect calorimetry is useful in prevention of overfeeding. Complications of overfeeding include the following:

- Hyperglycemia
- Liver compromise
- Increased CO_2 production from lipogenesis, which results in increased

ventilatory requirements

- Worsened outcome, as noted in a number of animal models and some human studies

NUTRITION FOR SPECIFIC DISEASE PROCESSES

Immune Function

Numerous commercial enteral formulas are marketed with the aim of modulating immune function as a nutritional therapy. Specific nutrients that may improve immune function include arginine, glutamine, ribonucleic acid, *w*-3 fatty acids, and vitamins A, C, and E. The *w*-3 fatty acids are considered immunostimulatory, whereas *w*-6 fatty acids are immunosuppressive. Therefore, providing both *w*-3 and *w*-6 fatty acids, resulting in a more balanced mixture of lipids, may improve overall immune function. Numerous clinical studies have compared immune-modulating formulas to standard formulas and reported that benefits vary but are not seen in medical ICU populations. Specific populations that have been found to benefit from the use of immune-modulating formulations are patients with traumatic brain injury, patients who have experienced trauma, and perioperative surgical ICU patients. The optimal amounts and combinations of immune-modulating nutrients remain unclear, as does whether different stages of illness and recovery require varied formulations. Further research is anticipated to clarify these issues.

Acute Lung Injury and Acute Respiratory Distress Syndrome

Several clinical trials have explored the effects of a specialized enteral formulation containing eicosapentaenoic acid, γ-linolenic acid, and antioxidants in patients with ARDS. Due to conflicting data from these trials, it is unclear whether these formulations are beneficial, so at present they cannot be routinely recommended as adjunctive therapy in acute lung injury or ARDS.

Acute Kidney Injury

Animal studies have demonstrated that early nutritional therapy improves outcomes after severe injury. In humans, recommendations for EN in acute kidney injury (AKI) include use of standard formulations. Many critically ill patients with AKI are hypermetabolic secondary to their comorbid conditions

and also have excessive losses of nutrients through dialysis techniques. Additionally, dialysis procedures themselves may increase nutritional demands. Protein intake should not be restricted; adequate nitrogen is required for healing and for other organ functions. Patients with AKI who are not undergoing dialysis should receive a minimum of 1.0 g of protein per kilogram of body weight per day. Critically ill patients with AKI who are undergoing intermittent hemodialysis should receive 1.2 to 1.5 g of protein per kilogram per day to compensate for expected losses via hemodialysis (ie, 3-5 g of amino acid per hour). Patients receiving continuous renal replacement therapies are expected to need more than 1.5 g of protein per kilogram per day. Fluid intake may be the major concern and can be limited with use of a calorie-dense formula (2 kcal/mL). Electrolyte levels (potassium, magnesium, phosphate) should be monitored carefully, and special enteral formulas with limited electrolytes may be indicated.

Hepatic Failure

Standard formulas are recommended for patients with liver dysfunction. Usually 1.0 to 1.2 g of protein per kilogram per day is needed to support repair and immune function; further limitation of protein is likely detrimental. No evidence is available to indicate that branched chain amino acids improve mental status in the ICU patient with hepatic encephalopathy who is receiving first-line treatments of lactulose and luminal-acting antibiotics. Data regarding EN in fulminant liver failure caused by viral hepatitis or drugs are insufficient to allow specific recommendations.

Inflammatory Bowel Disease

Patients with inflammatory bowel disease frequently have decreased nutrient intake, malabsorption, protein-losing enteropathies, and drug-nutrient interactions. Postpyloric enteral feeding of a peptide-based diet is usually well tolerated in patients with inflammatory bowel disease. Bowel rest is not necessary to achieve remission. EN should be attempted early, and PN should be used only when patients fail to tolerate EN.

Acute Pancreatitis

Numerous nutritional and metabolic alterations are induced by pancreatitis. Energy expenditure is widely variable. In the past, pancreatic rest by withholding

enteral nutrients was a common therapy for pancreatitis. However, the benefit of this practice was never proven in acute or chronic pancreatitis. Patients with mild acute pancreatitis should be advanced to an oral diet as tolerated, and their therapy should be modified if they develop complications. Patients with moderate to severe pancreatitis should begin EN with a standard formulation at trophic rates within 24 to 48 hours of admission. Studies have shown that early enteral feeding in the distal small bowel is associated with improved outcomes versus PN in patients with acute pancreatitis, so EN should be attempted before PN is initiated.

Wound Healing

Sufficient quantities of specific nutrients are needed for healing. Nutrients believed to be important in wound repair include vitamin A, vitamin C, zinc, arginine, and copper. Vitamin A provided at 7 to 8 times the RDI has been found to blunt impairments of wound healing induced by diabetes or steroids in animals but does not enhance wound healing in normal animals. Similarly, zinc and vitamin C are needed in sufficient quantities, but “pharmacological” or excessive amounts do not appear to further enhance healing. Pharmacological quantities of arginine improved wound healing in numerous animal studies and increased collagen deposition in humans. Copper is a required cofactor for collagen cross-linking. Requirements of most of these nutrients are believed to increase in critical illness; however, precise requirements are not established.

Morbid Obesity

The incidence and severity of obesity continues to increase worldwide. Early EN should be administered within 24 to 48 hours of ICU admission if patients cannot maintain volitional intake. Nonnutritional benefits of early EN are seen in obese patients as well as nonobese patients. Critically ill patients with morbid obesity should be provided high-protein hypocaloric nutrition during critical illness. Goals of this strategy include preservation of lean body mass, mobilization of adipose stores, and minimization of the metabolic complications of overfeeding. Specific details are reviewed in recent summaries and guidelines. Common initial goals are typically described as 11 to 14 kcal per kilogram of actual body weight per day and 2.5 g of protein per kilogram of IBW per day. Provision of this ratio of calories to nitrogen generally requires use of high-protein formulations as well as additional supplementation with modular protein. Indirect calorimetry may be of particular value, and for all classes of obesity the

goal of EN should be aimed to deliver 65% to 70% of measured energy expenditures.

Post Bariatric Surgery

Additional challenges can arise if a morbidly obese patient previously had bariatric surgical interventions, as these involve varied anatomic modifications. Such patients may have altered absorptive capabilities or vitamin deficiencies. Consideration of fluoroscopic placement of feeding tubes in such patients may be prudent to avoid complications if patients are unable to receive oral nutrition, especially if detailed surgical records are not readily available.

Multiple Organ Failure

Nutritional support is usually of marginal value in patients with multiple organ failure. For optimal benefits, nutritional therapy needs to be started before organ failure develops.

End-of-Life Considerations

Provision of artificial hydration and nutritional therapy is not obligatory in cases of futile care or end-of-life situations. Decisions regarding this should be made using evidence, best practices, and clinical judgement and experience and should include effective communication with appropriate decision makers, while maintaining respect for patient autonomy and dignity.

MONITORING RESPONSES TO NUTRITIONAL THERAPY

Visceral protein levels are no longer recommended to monitor response to nutritional support, because visceral protein levels are affected by nutritional intake as well as the clinical state (eg, inflammation, renal or hepatic dysfunction). Instead, the clinician should reevaluate the patient and medical condition to determine the adequacy of nutritional support. The utility of obtaining nitrogen balance should be considered, and indirect calorimetry studies for the individual patient should be repeated.

Nitrogen balance studies can determine the level of catabolism and may provide estimates of protein needs. Improvement in nitrogen balance over time suggests that nutritional support is adequate. However, nitrogen balance may improve as catabolism decreases, despite inadequate nutritional support. Reasonable indirect

calorimetry (metabolic cart) goals are to keep RQ between 0.8 and 1. An RQ greater than 1 suggests lipogenesis from excessive caloric intake; values of approximately 0.7 are found in starvation and reflect fat oxidation.

Diarrhea

Diarrhea is encountered in patients receiving EN and PN and is generally defined as greater than 500 mL of stool output per day (not merely as "loose stools"). **Table 4** provides recommendations for evaluation of diarrhea. The most common causes are medications and infections. Many elixir forms of medications contain sorbitol, which can cause diarrhea, especially if multiple doses are given. Once the specific causes of diarrhea have been evaluated, it can be treated with antimotility agents (ie, narcotics). Treatment with probiotic agents can be considered, but evidence of benefit in this setting is lacking.

Table 4. Causes and Evaluation of Diarrhea

Causes	Examples	Workup
Drugs	Sorbitol, antacids, H_2 blockers, antibiotics, lactulose, laxatives, quinidine, theophylline	No specific workup; discontinue any of these medications that are not absolutely necessary.
Infections	*Clostridium difficile*	Specific stool culture, *C difficile* toxin assay, sigmoidoscopy or colonoscopy for evidence of pseudomembranes.
	Infectious diarrhea (eg, typhoid fever, shigellosis)	Fecal leukocytes, culture.
	Other: bacterial overgrowth, parasites, systemic infection, HIV	As relevant (eg, look for ova and parasites, which rarely cause new diarrhea in critically ill).
Osmotic		Measure stool osmotic gap[a]; value >100 suggests osmotic diarrhea.
Impaction	May be secondary to narcotics	Rectal examination.
Other causes	Inflammatory bowel disease, pancreatic insufficiency, short gut syndrome	See other references for workup.

[a]Stool Osmotic Gap = Stool Osmolality – 2(Stool Sodium + Potassium).

SUMMARY

For optimal benefits and improved outcome, EN should be initiated within 24 to 48 hours of ICU admission in most critically ill patients.

Most critically ill patients should be given 25 kcal per kilogram of IBW per day and 1.5 g of protein per kilogram of IBW per day as initial goals. An exception is patients with morbid obesity, for whom hypocaloric high-protein strategies are recommended.

The use of PN is indicated only when EN is not possible. Many studies have shown superiority of EN over PN. Early supplemental PN administered with EN aimed at meeting energy expenditure goals is expensive, has not shown benefit, and may be detrimental.

Numerous studies suggest that early enteral feeding using immune-modulating formulas is associated with improved outcomes in specific ICU populations (traumatic brain injury, perioperative patients, trauma).

Use of protocols and nutrition support teams is recommended to help maximize efficacy and reduce risks associated with nutritional therapies of both EN and PN.

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CHAPTER 39

Critical Care Management of the Severely Burned Patient

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Key words: burn injury, resuscitation, inhalation injury, ventilator-associated pneumonia, nutritional support

Recent surveys have estimated that in the United States, approximately 450,000 patients per year suffer from burn injuries that necessitate medical treatment, with about 45,000 of those requiring hospitalization. The number of deaths per year from burns is estimated at 3,500, with most of those occurring at the scene or during initial transport. Therefore, most patients who arrive at a hospital with burn injuries will survive those injuries. The mortality rate for burn patients who arrive at a burn center is now less than 5%. However, a severe burn still presents a challenge to the clinician. A patient with a large burn injury will have derangements in almost every organ system. In addition, the immunosuppression associated with the insult will make the patient much more prone to a variety of hospital-acquired infections. The well-documented hypermetabolic response necessitates early nutritional and metabolic support to avoid severe protein-calorie malnutrition and the associated complications. This chapter highlights some of the most common issues associated with caring for these critically ill patients, including improvements in resuscitation, ventilatory management, and metabolic support.

The initial care of the severely burned patient involves airway assessment and management, resuscitation with lactated Ringer's solution based on the burn size, evaluation for significant inhalation injury, and topical wound care. Careful attention should be paid to preventing hypothermia as well as instituting early nutritional support with enteral feedings.

RESUSCITATION

Intravenous resuscitation of patients with major burns (>20% total body surface area [TBSA]) is standard of care in most developed countries. The volume of fluid required for resuscitation depends on the size of the burn. Over the years, many formulas have been developed that contain varying types of crystalloid and colloid fluids. One of the most commonly used protocols, the Parkland formula, uses lactated Ringer's solution at 2 to 4 mL/kg/%TBSA. This is the total predicted amount of fluid that is required over 24 hours, where the patient's weight is expressed in kilograms and %TBSA is the percentage of the body with either second- or third-degree burns. The initial calculated volume is then divided by 2, indicating the amount of fluid that typically would be required over the first 8 hours.

The general goal of resuscitation is to maintain adequate end-organ perfusion; however, the best way to determine whether this has been achieved remains somewhat controversial. In common practice, the end point of resuscitation is adequate urine output, which is 0.5 to 1.0 mL/kg. Unfortunately, urine output does not always reflect adequacy of resuscitation, especially in patients with preexisting renal insufficiency or renal failure, morbid obesity, very large burns, and electrical injury. In these cases, other indicators such as base deficit, lactate levels, cardiac output, stroke volume variability, and mixed venous or central venous oxyhemoglobin saturation levels have been used.

Most resuscitation formulas use crystalloid for the first 24 hours of resuscitation, with lactated Ringer's being the most popular. Glucose-containing solutions are not routinely used in the first 24 hours for fear of hyperglycemia and resultant osmotic diuresis. Colloid solutions, such as albumin, have traditionally not been used early, if at all. The fear is that these colloids will leak into the interstitium if used too early; therefore, when albumin is used, it is usually infused after the first 24 hours. There has been some interest in using fresh frozen plasma as part of early colloid resuscitation in large burns.

The vast majority of patients can be resuscitated with 2-4 mL/kg/%TBSA, with only 12% of patients requiring more than predicted. In past research, the most notable group of patients who required more fluid than predicted were those with very large burns and those who had inhalation injury in addition to burn. However, many recent studies have noted that burn patients are receiving significantly more fluid ("fluid creep") than would be predicted by the Parkland formula. Overresuscitation may lead to complications such as increased edema

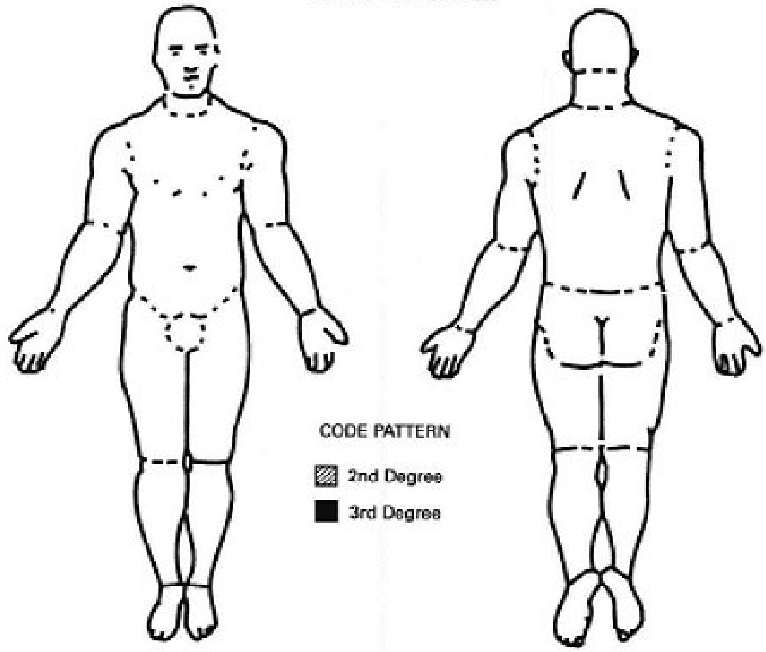
in the burned and nonburned areas, increased incidence of extremity and abdominal compartment syndromes, and prolonged ventilatory dependence.

Several explanations have been offered for the incidence of overresuscitation, and several potential interventions may be able to prevent fluid creep and its consequences. The first potential cause of fluid creep is overzealous initial resuscitation. First responders and inexperienced physicians tend to overestimate the burn size, leading to erroneous calculation of the fluid requirement. Another problem is that most physicians outside the burn unit are more familiar with trauma patients, who generally receive fluid more rapidly as a bolus. The US Army Institute of Surgical Research in San Antonio has confirmed that overzealous initial resuscitation translates into the requirement for more fluid later in the resuscitation phase. Therefore, accurate assessment of the burn size and early communication between first responders, physicians, and the burn center to guide early resuscitation can decrease overzealous fluid administration. The goal is to restrict the initial resuscitation to the lowest amount of fluid that still supports adequate urine output and to avoid overresuscitating or administering fluid as a bolus.

It is imperative to have an accurate assessment of the burn injury size to guide resuscitation. The most commonly used method is the Lund and Browder chart (**Figure 1**). When the burn patient arrives, the patient is carefully evaluated and the areas of second- and third-degree burns are noted on the chart. The resuscitation is then based on the area calculated. First-degree burn (simple erythema) is not used to calculate the TBSA burn.

Figure 1. Lund and Browder chart, used to assess burn injury size

BURN DIAGRAM



Weight (Adm.) _____ lbs. _____ kg.

Weight (Usual) _____ lbs. _____ kg.

Body surface area __________ m^2

Date of burn ________________

Date of discharge ______________

Etiology ____________________

Inhalation injury ❑ Yes ❑ No

Other associated injuries or diseases

____

____

BURN SIZE ESTIMATE

Area \ Age	Birth 1 yr.	1-4 yrs.	5-9 yrs.	10-14 yrs.	15 yrs.	Adult	Initial Estimate			Final Estimate		
							2°	3°	Total	2°	3°	Total
Head	19	17	13	11	9	7						
Neck	2	2	2	2	2	2						
Ant. Trunk	13	13	13	13	13	13						
Post. Trunk	13	13	13	13	13	13						
R. Buttock	2½	2½	2½	2½	2½	2½						
L. Buttock	2½	2½	2½	2½	2½	2½						
Genitalia	1	1	1	1	1	1						
R. U. Arm	4	4	4	4	4	4						
L. U. Arm	4	4	4	4	4	4						
R. L. Arm	3	3	3	3	3	3						
L. L. Arm	3	3	3	3	3	3						
R. Hand	2½	2½	2½	2½	2½	2½						
L. Hand	2½	2½	2½	2½	2½	2½						
R. Thigh	5½	6½	8	8½	9	9½						
L. Thigh	5½	6½	8	8½	9	9½						
R. Leg	5	5	5½	6	6½	7						
L. Leg	5	5	5½	6	6½	7						
R. Foot	3½	3½	3½	3½	3½	3½						
L. Foot	3½	3½	3½	3½	3½	3½						
Total												

Burn Data Sheet

Courtesy of Memorial Hermann Hospital–TMC.

Many clinicians may be reluctant to decrease fluid in a patient with a large burn who has adequate urine output, although these clinicians are willing to increase fluid in the setting of low urine output. This tendency alone leads to

overresuscitation. When clinicians start to use other end points of resuscitation such as cardiac output, lactate levels, or base deficit, many of which do not normalize in the first 24 hours, this can cause overresuscitation. Burn protocols may help guide nurses and physicians in proper resuscitation and avoid fluid creep.

Finally, other resuscitation alternatives have been explored to decrease the total volume infused. Hypertonic saline has been used for burn resuscitation and requires less volume. Pharmacological manipulation of inflammation and resuscitation has been noted to be a potential adjunct to decrease fluid requirements. High-dose vitamin C and anti-inflammatory drugs such as hydrocortisone or ibuprofen are a few of the potential agents that may help decrease the amount of fluid required. High-dose vitamin C was shown in at least one study to decrease the amount of fluid required in burn resuscitation. Interest has increased in the use of fresh frozen plasma, which has been shown to decrease the total volume of crystalloid infused and to decrease the incidence of abdominal compartment syndrome (ACS).

ACS deserves special mention. Secondary ACS is due to fluid sequestration in the peritoneal cavity and edema of the intra-abdominal organs. The treatment entails decreasing the amount of fluid infused, using paralytics to relax the abdominal wall muscles, administering diuretics, or initiating continuous venovenous hemofiltration to remove excess fluid. If ACS continues despite noninvasive therapy, the treatment is decompressive laparotomy. The mortality associated with ACS in burn patients requiring decompressive laparotomy is very high, ranging from 80% to 100%. A few reports have described percutaneously draining fluid in an attempt to relieve increased pressure without the morbidity and mortality of the laparotomy, but this approach is rarely used. The best treatment is to avoid the development of abdominal hypertension. This necessitates hour-to-hour titration of fluid based on urine output, monitoring of abdominal pressure via the bladder, and prompt institution of therapy to treat intra-abdominal hypertension before true compartment syndrome develops.

VENTILATORY MANAGEMENT

Critical care clinicians need to recognize the importance of mechanical ventilation in the burn ICU. For a variety of reasons, patients who have thermal injury are often at risk for airway compromise necessitating endotracheal intubation and mechanical ventilation. Smoke inhalation can cause significant damage to the oropharynx and upper airways, development of extensive whole-

body edema leading to airway loss, and hypoxia during the initial burn resuscitation, all of which may require endotracheal intubation and mechanical ventilation. In the days after burn injury, acute lung injury and acute respiratory distress syndrome (ARDS) can develop, necessitating mechanical ventilatory support.

INDICATIONS FOR INTUBATION

A thermally injured patient may require intubation and ventilator support to improve oxygenation, to remove carbon dioxide, or to protect gas exchange in the event of airway failure due to mucosal edema or altered mental status. Some of the more common indications for intubation include (1) respiratory distress from hypoxia and/or hypercarbia, (2) management of airway injury from smoke inhalation, and (3) airway protection in patients requiring large-volume fluid resuscitation or demonstrating rapidly progressing edema.

INHALATION INJURY

What Is Inhalation Injury?

Inhalation injury has many definitions but one that is generally accepted is "damage to the oro- and nasopharynx, pharynx, trachea, bronchi, alveoli, and systemic toxicity after inhalation of superheated gases, particulate matter, and by-products of combustion." Inhalation injury is rather complex because injury can damage any portion of the tracheal-bronchial tree. Inhalation injury can be classified into 3 types: (1) injury to the upper airways (ie, pharynx to the trachea), (2) injury to the lower airways and lung parenchyma, and (3) systemic toxicity due to inhaled toxic gases. Smoke inhalation is present in 20% to 30% of major burns and increases overall morbidity and mortality in burned patients. The lethality associated with smoke inhalation is related to the combination of its components (eg, particulate matter and gases) and the different levels of the respiratory tract affected. The dangerous gases found within smoke include sulfur dioxide, carbon monoxide, phosgene, acrolein, ammonia, hydrogen chloride, and hydrogen cyanide, all of which injure the lungs and may have systemic sequelae.

How Does Smoke Inhalation Injure the Respiratory Tree?

Upon inspiration of superheated gases, rapid heat exchange occurs on the moist

and well-vascularized mucosal surfaces of the upper airway. As thermal energy is exchanged, tissue injury leads to rapid mucosal swelling and increased transvascular fluid migration due to increased lymph and blood flow. Mucosal and submucosal injury precipitates the release of cytokines and inflammatory mediators, which worsens airway swelling to the point that it may lead to asphyxiation and death. Such rapid upper airway swelling is an urgent indication for intubation because the rate of swelling is unpredictable and can quickly progress to airway loss. As the components of smoke travel through the tracheobronchial tree, particulate matter and other toxins trapped within the smoke damage the mucosal lining, leading to sloughing of the ciliated epithelial cells and a further release of cytokines and inflammatory mediators that precipitate bronchospasm and transudation of large volumes of protein-rich fluid into the airways. Individually, each injury has minimal significance; however, the sloughed cells combine with the proteinaceous fluid that "leaks" into the airways, forming soft, bronchial casts that rapidly harden and may cause complete obstruction of alveolar units and small- and medium-caliber bronchi. The combination of these injuries can lead to a complete and nonsalvageable airway obstruction with certain death. In less severe cases, hypoxemia and hypercarbia may ensue as a result of shunting and ventilation-perfusion mismatching from the obstructed alveoli due to vasodilatory inflammatory mediators. Additional damage may occur in nonoccluded bronchi as a result of barotrauma and volutrauma as the ventilator tries to overcome the airway occlusions. The extensive lung injury caused by smoke inhalation predisposes these patients to the development of pneumonia and ARDS.

How Do We Detect Inhalation Injury?

The diagnosis of fire-related inhalation injury requires a combination of history and clinical findings. Much of the important information regarding risk factors for inhalation injury can be gathered from emergency medical service personnel. Some of these risk factors include a history of entrapment in a closed space fire, proximity to the fire, duration of smoke exposure, loss of consciousness at the scene, exposure to toxins, and extent of cutaneous burns. Physical examination is an important part of diagnosing inhalation injury; however, findings are often nonspecific and can be misleading. On examination, patients may have singed facial or nasal hair, carbonaceous sputum, hoarseness, and even stridor. Arterial blood gas analysis with co-oximetry should be performed at the beginning of the assessment and after the patient has been placed on 100% humidified oxygen to evaluate for acidosis, hypoxia, and carbon monoxide. Even if the history and

physical findings are consistent with inhalation injury, fiberoptic bronchoscopy remains the standard for evaluating patients with suspected inhalation injury. Bronchoscopy allows for visualization of the airways to determine the extent of mucosal edema, erythema, and blistering or mucosal sloughing as well as the presence of particulate matter. In addition, interest has increased in using multidetector computed tomography early in admission as an adjunct to bronchoscopy.

How Do We Treat This Injury?

Patients with suspected inhalation injury should undergo rapid airway assessment and be placed on 100% humidified oxygen via face mask. If hypoxia, hoarseness, stridor, or significant facial burns or edema is present, the clinician should immediately secure the patient's airway either by endotracheal intubation or by performing a surgical airway. Once the airway is secured, the patient should undergo bronchoscopy, which may be diagnostic and therapeutic in patients with inhalation injury; however, saline lavage is not recommended to remove particulate matter because this procedure can push particles into the alveoli and wash away alveolar surfactant. Serial bronchoscopy should be considered in patients with severe inhalation injury and for pulmonary toilet in patients with extensive sloughing and early cast formation. Ventilator management should include lung-protective strategies such as low tidal volume ventilation (6-8 mL/kg), open-lung strategies using high positive end-expiratory pressure in a manner similar to that used in the ARDS Network trial, permissive hypercapnia, and various lung recruitment maneuvers. A recent development in mechanical ventilatory support for patients with severe inhalation injury is the introduction of high-frequency percussive ventilation (HFPV) by a volumetric diffusive respiration ventilator. HFPV is a ventilator mode that combines features of both conventional and jet ventilation with a standard pressure-controlled breath superimposed on a high-frequency (200-600 breaths per minute) delivery of breaths, providing for a percussive element to standard pressure control ventilation (10-30 breaths per minute). The purported advantages are to loosen airway exudate and casts for better pulmonary toilet and to provide adequate gas exchange at lower airway pressures. In initial studies of burned patients with an associated inhalation injury, HFPV was used as a salvage therapy in some patients and as primary therapy in others. Patients treated with HFPV were found to have improved oxygenation and a lower rate of pneumonia. An improvement in mortality was also noted in burned patients with inhalation injury treated with HFPV compared with historical controls.

Additional studies have shown significant decreases in the work of breathing and lower inspiratory pressures in addition to improvements in oxygenation and decreased rate of pneumonia. The data seem compelling that HPFV is efficacious in the treatment of inhalation injury and should be given consideration as a first line treatment modality for patients with severe inhalation injury. Last, intensivists should consider the use of aerosolized agents to improve the pulmonary toilet. Inhaled β-agonists (ie, albuterol) may be required in patients who develop bronchospasm due to lower airway injury. Therapy with aerosolized heparin and/or acetylcysteine has also been investigated in patients with inhalation injury. The mechanism of action of these agents is believed to be reduction of free radicals and inhibition of fibrin cast formation in the airways. The combined use of these agents in burned patients with inhalation injury has been shown to reduce the number of ventilator-days, decrease the incidence of atelectasis, reduce the incidence of reintubation for progressive respiratory failure, attenuate acute lung injury and progression to ARDS, and decrease mortality. The early use of bronchoscopy to evaluate inhalation injury is critical in determining the need for nonconventional ventilation, serial bronchoscopy for pulmonary toilet, and the addition of inhaled heparin to the inhalation injury management algorithm.

VENTILATOR-ASSOCIATED PNEUMONIA

Infectious complications have become the predominant cause of death in thermally injured patients since the introduction of effective fluid resuscitation protocols. In addition, the introduction of topical antimicrobials into burn care has led to a paradigm shift in the infectious complications. As a result, pneumonia has become a more significant contributor to morbidity and mortality due to the ability to control burn wound sepsis with topical antibiotics. Thermally injured patients requiring endotracheal intubation and mechanical ventilation are at an increased risk of developing ventilator-associated pneumonia (VAP); however, little is known about the incidence of VAP in thermally injured patients requiring mechanical ventilation, and data from other ICU patients have been extrapolated to burn patients.

The risk of developing VAP begins during endotracheal intubation. Intubation may occur in the prehospital or field setting, at an outside hospital, in the emergency department, or in the ICU. Patients with concomitant thermal injury and trauma requiring urgent intubation in the field or the emergency department have an increased risk of developing VAP. It is believed that aspiration occurs

during this procedure. Therefore, intubation of burn patients should be performed using techniques that decrease the risk of aspiration (ie, rapid sequence intubation with cricoid pressure).

The respiratory tract's protective mechanisms fail as a result of both the burn injury and intubation necessitated by inhalation injury or airway edema. The development of nosocomial pneumonia in burn patients occurs by mechanisms similar to those of other patients who require endotracheal intubation and mechanical ventilation. Microorganisms are believed to enter the lower airways through one of four routes: (1) aspiration of secretions from the oropharynx or refluxed from the gastrointestinal tract that contain microorganisms (most common), (2) direct extension of a contiguous pleural space infection, (3) inhalation of contaminated air or medical aerosols, or (4) the hematogenous spread of microorganisms from remote sites of infection (ie, burn wounds, intravascular devices, or urinary catheters). Intubated burn patients can also develop VAP from bacteria endemic to the ICU that are not part of the normal oropharyngeal or gastrointestinal flora. These bacteria are often transferred to the patient from the hands of healthcare workers, from contaminated devices, via medical aerosols, or as a result of tracheostomy, which allows bacteria to bypass the oropharynx.

Bacterial pneumonia tends to be the most common cause of VAP in burn patients. The time that VAP occurs often indicates the type of microorganisms responsible for its evolution. Early VAP occurs within the first 4 days of admission, carries a better prognosis, and is most frequently due to antibiotic-sensitive organisms. Gram-positive bacteria (ie, *Staphylococcus* and *Streptococcus* species) are the common causative organisms in early VAP. Late-onset pneumonia occurs 5 or more days after initiation of intubation and is predominantly caused by multidrug-resistant gram-negative organisms and methicillin-resistant *Staphylococcus aureus*. *Pseudomonas aeruginosa* is the most common cause of late VAP; it has a high degree of multidrug resistance and an associated mortality rate of up to 80% in burn patients.

The clinical diagnosis of VAP is usually made when the patient has a new or progressively worsening infiltrate on chest radiograph and at least 2 of the following: fever, purulent sputum, or leukocytosis. This method of diagnosis is not applicable to burn patients because they are often febrile, tachypneic, and tachycardic and have elevated white blood cell counts, making it hard to determine whether their symptoms are related to pneumonia or are simply their baseline. Burn intensivists have looked to the use of a bacteriological method of

diagnosis, often in combination with some aspects of the clinical approach. The bacteriological approach involves the use of fiberoptic bronchoscopy to obtain bronchoalveolar lavage specimens that are submitted for Gram stain and quantitative cultures. The advantages of this method include increased specificity and the ability to identify the exact causative organism, allowing for antibiotic de-escalation. Unfortunately, these procedures may not be available in all cases, and they cannot be performed in patients with severe hypoxia. The use of bronchoscopy and quantitative cultures to diagnose VAP in burn patients has been endorsed by the American Burn Association.

An area of great controversy in treating VAP in burn patients is the duration of antibiotic therapy. Many physicians will treat VAP for either 7 or 14 days; however, studies evaluating the treatment of VAP for either 8 or 15 days found no difference in outcomes. The important factor was use of the appropriate antibiotic regimen for treatment. Guidelines from the American Burn Association recommend treating VAP caused by pan-sensitive microorganisms with 8 days of antibiotics, but with VAP caused by multidrug-resistant organisms should be treated with 15 days of antibiotics.

METABOLIC AND NUTRITIONAL SUPPORT

The human body is able to endure a wide spectrum of injuries with minimal physical and metabolic sequelae; however, severe burn injury has been described as the "greatest possible state of physiological stress." Burns can induce a significant hypermetabolic response that leads to endocrine dysfunction, immune compromise, catabolism, and a persistent inflammatory state. This intense hypermetabolic and catabolic state can persist for weeks to months and in some cases up to 2 years.

In general, the severely burned patient undergoes a metabolic response characterized by 2 unique phases: The first is a hypodynamic "shock state" (or "ebb phase"), and the second is a hyperdynamic-catabolic state ("flow phase") associated with changes in body temperature and alterations in metabolism and substrate cycling. The ebb phase typically lasts from 24 to 72 hours and then transitions to the hyperdynamic flow phase. The flow phase can be identified by supraphysiological cardiac output, elevated body temperature, supranormal oxygen and glucose consumption with subsequent increases in carbon dioxide production, increased urinary nitrogen losses, altered glucose metabolism, futile substrate cycling, and accelerated tissue catabolism. This hypermetabolic state is believed to be a consequence of excessive and unabated release of catabolic

hormones such as catecholamines, glucagon, and cortisol. Catecholamines driving the intense metabolic response to thermal injury require a large quantity of available substrates to maintain this hyperdynamic state. This is accomplished by increased utilization of amino acids via increased protein catabolism, which has been found to be 2 times greater in thermally injured patients compared with normal, fasted patients. To further produce a large energy supply, the cellular synthetic machinery transfers from a balanced anabolic-catabolic, homeostatic state to a hypercatabolic state requiring increased quantities of substrates not usually used for energy production. As a result, skeletal muscle is rapidly broken down into amino acids to maintain sufficient glucose production to keep up with the increased metabolic demands (ie, an increased resting metabolic rate [RMR]). The RMR is directly affected by the severity of the burn and increases in a curvilinear fashion; large burns (>40% TBSA) increase the RMR by 180%. If the energy requirements needed to attain and maintain this elevated RMR are met by skeletal muscle amino acids, which are shunted to the liver for gluconeogenesis, how would an intensivist determine the caloric and protein requirements of a critically ill burn patient?

Mathematical equations and formulas have been developed for estimating energy need in burned patients. Unfortunately, all formulas are inaccurate when compared with measurement of metabolic rate by indirect calorimetry. Indirect calorimeters measure oxygen consumption and carbon dioxide production to derive energy utilization, and these values can be useful in determining resting energy expenditure (REE). If indirect calorimetry is not available, the current recommendation for feeding thermally injured patients is 30 to 40 kcal/kg per day. The enteral feeding formula must supply enough nonprotein calories to decrease the use of protein for energy. Carbohydrates are an excellent source of nonprotein calories, and it is recommended that carbohydrates comprise at least 60% of the calories administered without surpassing 400 g/d or 1,600 kcal/d. The other important source of nonprotein calories is fat, which supplies 9 kcal/g. Lipids should be limited to ∼12% to 15% of the nonprotein calories. Clinicians should monitor immune function, wound healing, feeding tolerance, respiratory function, and serum triglycerides before increasing the amount of lipids used. Enteral feeding formulas should contain essential fatty acids such as linoleic and linolenic acids because they improve feeding tolerance and immune response. Protein is the final component of caloric needs and should make up approximately 20% to 25% of total calories provided. Reports in the burn literature vary regarding the exact amount of protein required daily, but the acceptable range is 2.0 to 2.5 g/kg per day, and this protein must include

essential amino acids. A positive nitrogen balance is essential in preventing further breakdown of skeletal muscles; however, care must be taken when prescribing protein in patients with renal or hepatic failure.

Supplementation of vitamins, antioxidants, and minerals in burn patients is also important. Vitamins A, C, D, and E need to be appropriately supplemented, as should zinc, copper, and selenium, all of which play vital roles in wound healing, immune and enzymatic function, and bone support. Enteral nutrition should be initiated after fluid resuscitation has begun; early introduction of enteral feeding has been shown to decrease the hypercatabolic response, thereby augmenting the catecholamine and glucagon surge, decreasing weight loss, improving caloric intake, stimulating insulin secretion, improving protein retention, and decreasing duration of inpatient stay. Enteral nutrition by either gastric or postpyloric feeding tube is preferred over the use of parenteral nutrition (given the known association of parenteral nutrition with increased infection rates and mortality).

Intensivists taking care of burn patients should routinely assess their nutritional status. Nutritional assessment begins with establishing the current nutritional and metabolic status of the patient and then determining the extent of the burn injury. These two factors are important in the timing of nutritional support intiation and the calculation of ongoing caloric requirements through daily assessments of caloric and protein intake. Daily nutritional assessment begins at the bedside, where the clinician assesses daily weight and evaluates burn wounds for healing, both of which are excellent indicators of the patient's nutritional state. Nutritional status can be followed also by monitoring the biochemical marker for protein malnutrition, prealbumin. Prealbumin is less affected by thermal injury than are other serum proteins (ie, albumin), even though it is produced mainly in the liver, and it has one of the highest ratios of essential to nonessential amino acids of any protein in the body, making it a distinct marker for protein anabolism. Prealbumin levels are more sensitive because the half-life is only a few days, and a value of 15 mg/dL reflects early malnutrition and the need for nutritional support.

A persistent hypermetabolic state is unsustainable and can have detrimental effects on outcomes. Two strategies that can be used to calm the catabolic torrent are (1) decreasing the catabolic response through antagonism and (2) stimulating anabolism through pharmacological means. First, the catabolic response can be antagonized by preventing and aggressively treating sepsis, performing early burn excision and grafting, and strictly maintaining a core body temperature between 38°C and 38.5°C (between 100.4°F and 101.3°F). These measures

prevent further worsening of the catabolic state and, to some degree, will move the patient's REE closer to the preinjury state. Catabolism can also be antagonized pharmacologically through the use of β-blockers, which inhibit the effects of catecholamines and thereby lessen the hypermetabolic response. Propranolol, a nonselective β-blocker, has been the β-blocker of choice. The mechanism by which β-blockade augments the hypermetabolic response is by reducing supraphysiological thermogenesis, tachycardia, myocardial oxygen demand and cardiac work, and REE. Muscle catabolism is also slowed by the use of β-blockade. β-Blockade has been shown to improve net muscle protein synthesis and increase lean body mass in children with acute severe burns. The dose of propranolol should be adjusted until the heart rate has decreased by 20%. These benefits are believed to be the same in adults, even though no prospective trials have examined the use of β-blockade in adult burn patients.

The other method used to ameliorate the adverse effects of a hypercatabolic state is the introduction of pharmacological agents that convert catabolism to anabolism. Recombinant human growth hormone (rHGH) was one of the first anabolic agents found to abate the hypermetabolic response seen in thermal and nonthermal injury. The benefits of using this hormone include a decrease in total body catabolism, improved protein synthesis in skeletal muscles, accelerated donor site and wound healing, improved immune response, diminished synthesis of hepatic acute phase proteins, and promotion of linear bone growth. Despite all of the benefits, rHGH can worsen hypermetabolism and thermogenesis by overstimulation of gluconeogenesis, can precipitate hyperglycemia and insulin resistance, and can increase mortality rates in adults with nonthermal trauma. The use of rHGH has been studied mainly in children, but it is used in adults with the belief that similar benefits exist. Both insulin-like growth factor 1 and IV insulin have been used for their anabolic effects. Insulin-like growth factor 1 is a small peptide that is synthesized by the liver, is secreted into the bloodstream under the control of growth hormone, and circulates in the serum tightly bound to high-affinity proteins. Insulin-like growth factor 1 has sparked interest because it has potent anabolic effects without the catabolic side effects of growth hormone. Most of the research involving the use of insulin-like growth factor 1 has been conducted in the pediatric burn population, where this agent has demonstrated an ability to decrease protein oxidation, diminish muscle catabolism, restore gut mucosal integrity, and promote glucose uptake with no changes in REE. Insulin itself has been found to be useful in the control of hypercatabolism. Hyperglycemia, a common sequela of hypermetabolism that is often seen in thermally injured patients, has been shown to increase protein

catabolism, decrease wound healing and split-thickness skin graft take, and even increase mortality. The infusion of low-dose (7-15 U/h) regular insulin promotes increases in lean body mass and shortens length of stay without increasing caloric requirements. In addition, insulin has been shown to have anti-inflammatory properties and may provide some benefit in decreasing the massive inflammatory response seen in severe thermal injury. The final pharmacological agent that has been shown to effectively decrease hypercatabolism is an anabolic steroid called oxandrolone. It has been well studied, has fewer side effects than other anabolic agents, and has anabolic effects that are 10 times greater than those of testosterone. Several investigators have demonstrated that oxandrolone improves muscle synthetic activity, increases expression of anabolic genes in muscle, and increases net muscle protein synthesis with subsequent improvement in lean body mass composition. Other benefits of oxandrolone include its use in both the acute and recovery phases of burn injury, reasonable cost, and oral administration. Despite all of its benefits, oxandrolone can cause virilization in females, hepatic dysfunction, hirsutism, and other androgenic effects similar to those seen in patients receiving testosterone. The most common side effect is a transient elevation in liver function tests that often returns to baseline with discontinuation of the medication.

SUMMARY

Severe thermal injury is a potent inducer of hypercatabolism and causes loss of lean muscle mass, poor wound healing, and increased susceptibility to infection. A patient who survives the early hypodynamic shock state will enter a hypermetabolic state that can be controlled and eventually defeated. Intensivists need to initiate early and appropriate enteral feeding, monitor nutritional status daily, and use surgical, environmental, and pharmacological adjuncts to decrease the hypermetabolic response.

SUGGESTED READING

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CHAPTER 40

Poisoning and Toxicology in the Critically Ill

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More than 20,000 people die of overdoses each year in the United States, and ICU clinicians should be able to anticipate and manage complications of overdoses. In many cases, only supportive care is necessary until the effects of the toxin diminish. However, some poisonings require specific antidotes or interventions to decrease morbidity and mortality. General management principles of poisonings and substance abuse that are pertinent to intensive care are presented here, as well as interventions for specific overdoses. Little evidence-based information is available in toxicology, and current recommendations are based on animal data, volunteer studies, case reports, pharmacological data, and consensus opinion.

RESUSCITATION AND STABILIZATION

The initial priorities in caring for a poisoned patient are airway, breathing, and circulation. Oxygenation, ventilation, and airway patency should be assessed to determine the need for supplemental oxygen or intubation. Hypotension from toxins should be treated initially with isotonic fluids rather than vasopressor agents. In patients with depressed level of consciousness of unknown origin, the following interventions should be considered: (1) 50% glucose (25-50 g IV), (2) thiamine (100 mg IV), and (3) naloxone (0.4-2 mg IV), especially with findings of miosis and respiratory depression. Flumazenil administration is not routinely recommended.

DIAGNOSIS

Identifying the exact substance involved in an overdose or poisoning never takes precedence over resuscitation and stabilization. However, the initial evaluation may identify characteristic signs and symptoms that will enable a specific diagnosis and institution of optimal therapy. The absence of symptoms on initial examination does not preclude potential deterioration and development of more severe symptoms.

HISTORY

Accurate information regarding the substance, amount, and time of ingestion should be collected to assess the clinical significance of presenting symptoms and to interpret toxin levels. Identifying the form of drug involved (regular or sustained release) and the chronicity of use is also helpful. The clinician should determine what drugs the patient had access to, including cardiac medications, antidepressants, and narcotics.

PHYSICAL EXAMINATION

Patient vital signs and the neurological examination are particularly helpful in the initial evaluation (**Tables 1 and 2**). Although the initial neurological examination may have significant findings, clinicians should follow changes in neurological function over time. The evaluation should include an assessment of level of consciousness, pupillary reactivity, ocular movements, bowel sounds, and motor responses. Abnormal findings may characterize the poisoning into a "toxidrome," which may suggest appropriate diagnostic evaluation and therapy (**Table 3**).

Table 1. Clues to Diagnosis in Poisoning: Vital Signs

Vital Sign	Increased	Decreased
Blood pressure	Amphetamines, cocaine	Antihypertensives
	Anticholinergics	Cyanide
	Bath salts	Cyclic antidepressants
	Ephedrine	Ethanol
	Sympathomimetics	Narcotics
	Synthetic cannabinoids	Organophosphates, carbamates
		Sedatives, hypnotics
Heart rate	Amphetamines, cocaine	Barbiturates

	Anticholinergics Bath salts Carbon monoxide Cyanide Cyclic antidepressants Ethanol Sympathomimetics Theophylline Synthetic cannabinoids	β-Blockers Calcium channel blockers Cholinergics Digitalis glycosides γ-Hydroxybutyrate Organophosphates, carbamates Sedatives, hypnotics
Respiratory rate	Amphetamines Anticholinergics Carbon monoxide Narcotics Hydrocarbons Organophosphates, carbamates Salicylates Theophylline	Alcohols Barbiturates Sedatives, hypnotics γ-Hydroxybutyrate Narcotics
Temperature	Amphetamines, cocaine Anticholinergics β-Blockers Cyclic antidepressants Salicylates Sympathomimetics Theophylline	Barbiturates Carbon monoxide Ethanol Hypoglycemic agents Narcotics Sedatives, hypnotics

Table 2. Clues to Diagnosis in Poisoning: Neurological Findings

Neurological Sign	Possible Agent
Pupils Pinpoint (miotic)	 Barbiturates (late) Cholinergics Narcotics (except meperidine) Organophosphates Phenothiazine Phencyclidine

Dilated (mydriatic)	Alcohol Anticholinergics Antihistamines Barbiturates Ethanol Meperidine Phenytoin Sympathomimetics
Nystagmus	Alcohol Carbamazepine Carbon dioxide Phencyclidine Phenytoin Sedatives, hypnotics
Seizures	Amphetamines Anticholinergics Carbon monoxide Cocaine Cyanide Cyclic antidepressants γ-Hydroxybutyrate Isoniazid Lithium Organophosphates Phencyclidine Phenothiazine Salicylates Strychnine Theophylline

Table 3. Toxidromes

Cholinergic	SLUDGE: salivation, lacrimation, urination, defecation, gastrointestinal upset, emesis. Also, bronchorrhea, bradycardia, fasciculations, confusion, miosis.
Anticholinergic	Dry skin, hyperthermia, mydriasis, tachycardia, delirium, thirst, urinary retention
Sympathomimetic	Hypertension, tachycardia, seizures, central nervous system excitation, mydriasis, diaphoresis
Narcotic	Miosis, respiratory depression, depressed level of consciousness, hyporeflexia
Sedatives, hypnotic	Depressed level of consciousness, respiratory depression, hyporeflexia, hypotension

LABORATORY EXAMINATION

Laboratory data supplement the history and physical examination. An arterial blood gas (ABG) measurement will detect hypoxemia, hypercarbia, and acid-base disorders. In combination with electrolytes, an increased anion-gap acidosis may be diagnosed. Detection of an osmolal gap (>10 mOsm/kg) by comparison of measured osmolality with calculated osmolality—[(2 × Sodium) + (Glucose/18) + (Blood Urea Nitrogen/2.8)]—can indicate the presence of methanol, ethanol, ethylene glycol, acetone, or isopropyl alcohol. An electrocardiogram (ECG) should be obtained in unstable patients and when cardiotoxic drug ingestion is suspected. Qualitative urine toxicology screens report only the presence or absence of a substance and are limited to a small number of drug groups. Qualitative screens have minimal or no impact on the initial management of poisoned patients. Quantitative serum or plasma analyses can direct specific therapies in selected cases. Acetaminophen levels are particularly helpful in the patient with unknown poisoning or multiple drug ingestions. Other quantitative levels that may be useful include carbamazepine, carboxyhemoglobin, ethanol, phenytoin, lithium, digoxin, valproic acid, and cyclic antidepressant levels. Although cyclic antidepressant levels may confirm antidepressant ingestion, they correlate poorly with toxicity.

INTERVENTIONS TO DECREASE ABSORPTION AND ENHANCE ELIMINATION OF TOXINS

Following initial stabilization, other interventions can be considered to decrease absorption of toxins from the gastrointestinal (GI) tract or to enhance elimination.

Decreased Absorption

GI decontamination techniques include gastric emptying procedures (induced emesis, gastric lavage), adsorption of drugs (activated charcoal), and increasing the rate of transit through the GI tract (cathartics, whole bowel irrigation).

Induced emesis with ipecac is not recommended. Gastric lavage should not be used routinely and should be considered only in life-threatening situations when instituted within 1 hour of ingestion. Studies have failed to confirm any outcome benefit of lavage, even if performed within 1 hour of ingestion. Lavage is contraindicated in acid or alkali ingestions, because of possible esophageal perforation, and in the presence of severe bleeding diathesis. Other

complications include aspiration pneumonitis and cardiovascular instability.

Efficacy of activated charcoal administration has not been proven, but it can be considered for orally ingested poisons. Potential benefit is most likely if charcoal is administered within the first hour after ingestion. The appropriate dose of charcoal (1 g/kg) can be administered by an orogastric or nasogastric tube if necessary. Multiple doses may be appropriate for carbamazepine, dapsone, phenobarbital, quinine, or theophylline toxicity. Repeat charcoal doses should not contain a cathartic, and adequate gastric emptying must be ensured before administration of subsequent doses. Substances not adsorbed by activated charcoal include iron, lithium, cyanide, strong acids or bases, alcohols, and hydrocarbons. The only contraindication to the use of charcoal is known or suspected GI perforation.

Cathartics such as sorbitol have been administered in combination with charcoal, based on the assumption that they shorten GI transit time and limit drug absorption. However, evidence of efficacy is lacking. Cautious use is indicated with elderly patients because electrolyte abnormalities can ensue due to diarrhea.

Whole bowel irrigation involves large volumes of polyethylene glycol electrolyte solution (1-2 L/h) administered through a nasogastric tube to mechanically cleanse the bowel. This method has been suggested for ingestions of substances that are not adsorbed by activated charcoal, ingestions of sustained-release or enteric-coated products, and ingestions of illicit drug packets. However, no evidence of efficacy is available. Contraindications to this intervention include ileus, GI obstruction or perforation, hemodynamic instability, and intractable vomiting; relative contraindications include central nervous system (CNS) or respiratory depression and inability to cooperate.

Enhanced Elimination

Alkaline diuresis with sodium bicarbonate is effective in enhancing the elimination of barbiturates, primidone, and salicylates but may induce hypokalemia. Acidification of urine is not recommended.

Dialysis can be considered for life-threatening ingestions involving water-soluble substances of low molecular weight, including alcohols, amphetamines, phenobarbital, lithium, salicylates, theophylline, and thiocyanate. Hemoperfusion is useful with the same compounds that are dialyzable; it involves passing blood through a filtering device that contains charcoal or a

synthetic resin as an absorbent. Charcoal hemoperfusion may be preferred for eliminating carbamazepine, phenobarbital, phenytoin, and theophylline. Use of continuous venovenous hemoperfusion in poisoning has been reported on a limited basis.

Intravenous lipid emulsion (ILE) therapy has been used with varying success in some overdoses. It has been reported to reverse cardiovascular and neurological effects from acute toxicity with some lipophilic drugs. The exact mechanism of action for ILE is unknown but is thought to be related to the "lipid sink" phenomenon in which lipophilic drugs are pulled from the plasma and tissue. Doses vary in case reports, but the typical dose includes a bolus of 1.5 mL/kg of 20% to 30% ILE followed by an infusion of 0.25 to 0.5 mL/kg/min for 30 to 60 minutes. Positive outcomes have been consistently demonstrated with local anesthetic toxicity (bupivacaine, lidocaine), but case reports have noted positive results with calcium channel blockers (verapamil, diltiazem), β-blockers (atenolol, propranolol), and psychotropic agents (amitriptyline, venlafaxine). ILE is not recommended as a first-line intervention.

SPECIFIC THERAPY

Although management of many toxic ingestions involves only supportive care and the nonspecific therapy outlined here, specific interventions or antidotes are indicated for some toxins (**Table 4**). Specific drug poisonings are discussed in detail below.

Table 4. Antidotes and Interventions for Specific Toxins

Toxin	Antidote or Intervention
Acetaminophen	*N*-acetylcysteine
Amphetamines	Benzodiazepines
Arsenic, mercury, gold, lead	Dimercaprol
β-Blocker	Glucagon, calcium,[a] pacing
Bath salts	Benzodiazepines
Benzodiazepines	Flumazenil
Calcium-channel blocker	Calcium, glucagons, pacing, insulin euglycemia
Carbon monoxide	100% oxygen, hyperbaric oxygen
Cocaine	Benzodiazepines
Coumarin derivatives	Vitamin K_1

Cyanide	Nitrites, thiosulfate, hydroxocobalamin
Cyclic antidepressants	Blood alkalinization
Digoxin	Digoxin-specific Fab
Ethylene glycol	Ethanol, fomepizole
Heparin	Protamine
Iron	Deferoxamine
Isoniazid	Pyridoxine
Lithium	Hemodialysis
Methanol	Ethanol, fomepizole
Narcotics	Naloxone
Nitrites	Methylene blue
Oral hypoglycemic agents, insulin	Glucose 50%, octreotide
Organophosphates, carbamates	Atropine, pralidoxime
Salicylates	Urinary alkalinization, hemodialysis
Synthetic cannabinoids	Benzodiazepines
Theophylline	Multiple-dose charcoal, hemoperfusion

[a]Experience with calcium is limited, but its use may be considered.

Adapted with permission. Zimmerman JL. Critical care poisonings. In: Zimmerman JL, ed. *Seventh Critical Care Refresher Course*. Des Plaines, IL: Society of Critical Care Medicine; 2003:113.

Acetaminophen

Acetaminophen levels should be obtained in all multiple drug overdoses at 4 hours or more after ingestion. Levels plotted on the Rumack-Matthew nomogram determine the need for *N*-acetylcysteine (NAC) therapy in single acute ingestions. NAC is most effective when initiated in the first 8 hours following ingestion but is recommended up to 24 hours after a significant ingestion. Oral NAC is administered as a 68-hour regimen with a loading dose of 140 mg/kg followed by 17 oral maintenance doses of 70 mg/kg every 4 hours. Given the strong sulfur smell, mixing oral NAC in a soft drink and drinking through a straw can increase palatability and tolerability while decreasing nausea and vomiting. If vomiting occurs within 1 hour of dose administration, the dose should be repeated. Alternatively, intravenous NAC is administered as a 21-hour continuous infusion with a loading dose of 150 mg/kg infused over 1 hour followed by 50 mg/kg infused over 4 hours and then 100 mg/kg infused over 16

hours. Anaphylactoid reactions can occur with IV NAC. It is also reasonable to administer NAC more than 24 hours after ingestion if toxic levels of acetaminophen are present. Late administration of NAC is indicated in fulminant hepatic failure caused by acetaminophen toxicity. No firm guidelines are available for administration of NAC in chronic ingestions or multiple ingestions over time. If transaminases are elevated at the time of presentation (>50 U/L) or the acetaminophen level is greater than 10 μg/mL (>10 μmol/L), a course of NAC should be strongly considered. Activated charcoal can bind to acetaminophen in the GI tract directly or through enterohepatic circulation and should be considered for administration if the ingestion is within 1 hour of presentation or with significant ingestions.

Alcohols

Ethylene glycol, methanol, isopropyl alcohol, and propylene glycol ingestions can result in significant morbidity and mortality. Clinical manifestations, metabolic derangements, and management are similar for ethylene glycol and methanol. Symptoms include pulmonary edema, hypotension, abdominal pain, nausea, vomiting, ataxia, seizures, and coma. An anion-gap acidosis and an osmolal gap are common in severe cases. An anion-gap acidosis may not be present initially if sufficient time has not elapsed for metabolism to toxic acids or if high levels of ethanol prevent metabolism of other alcohols. An osmolal gap may not be present in late presentations if the alcohol has already been metabolized to acids. Calcium oxalate crystals in the urine can suggest ethylene glycol ingestion. Visual disturbances (blurred vision, photophobia, blindness, optic disc hyperemia) are clues to methanol toxicity; however, some clinically relevant symptoms can be delayed up to 24 hours after methanol ingestion. Many institutions are unable to determine ethylene glycol or methanol blood levels in a timely manner, and treatment is initiated on the basis of clinical history and acid-base status.

To inhibit metabolism into toxic metabolites, treatment for ethylene glycol and methanol toxicity includes ethanol or fomepizole. Ethanol is preferentially metabolized by alcohol dehydrogenase over other alcohols. Ethanol orally or IV is dosed to maintain blood levels at 100 to 150 mg/dL, which can cause or worsen CNS depression. Fomepizole is a competitive inhibitor of alcohol dehydrogenase that does not cause CNS depression and allows for alcohol excretion through renal elimination or dialysis. Given the ease of use and reduction in medication errors compared with ethanol, fomepizole may be

preferred for treatment of ethylene glycol and methanol poisoning. Vitamin supplementation (thiamine, folate, pyridoxine, and multivitamins) should be considered in all alcohol ingestions, and folinic acid or folic acid (50 mg IV every 4-6 hours for 24 hours) should be considered in methanol ingestions to provide the cofactor for formic acid elimination. IV fluids should be used to maintain urine output, and hemodialysis should be instituted for visual impairment, significant or refractory acidosis, or alcohol levels greater than 25 mg/dL.

Isopropyl alcohol is more potent than ethanol and results in similar clinical manifestations at lower doses. Intoxication of hospitalized patients by ingestion of hand sanitizers that contain isopropyl alcohol in high concentrations has been reported. Isopropyl alcohol ingestions are characterized by an osmolal gap and ketone production (acetone) but no metabolic acidosis. Treatment is supportive. Hemodialysis is reserved for evidence of hypoperfusion and failure to respond to supportive therapy.

Propylene glycol toxicity can develop in critically ill patients receiving high doses of IV medications containing propylene glycol, including lorazepam, diazepam, phenobarbital, pentobarbital, and sulfamethoxazole-trimethoprim. Common manifestations of propylene glycol accumulation are anion-gap metabolic acidosis and increased osmolal gap. Additional toxicities include renal dysfunction, hemolysis, cardiac arrhythmias, seizures, and CNS depression or agitation. For lorazepam, accumulation can occur when doses exceed 0.1 mg/kg/h or after long periods of lorazepam infusion (>3 days). The treatment of choice is to stop the offending agent, but hemodialysis may be considered if severe renal dysfunction develops.

Amphetamines and Methamphetamines

Amphetamines, methamphetamines, and related agents are drugs of abuse that cause release of catecholamines leading to a sympathomimetic toxidrome (**Table 3**). Hallucinations (visual and tactile), hyperthermia, and acute psychosis are frequently observed. Acute adverse consequences include myocardial ischemia, arrhythmias, seizures, intracranial hemorrhage, stroke, rhabdomyolysis, renal failure, necrotizing vasculitis, and death. Dilated cardiomyopathy can result from long-term use. Methamphetamine hydrochloride in a crystalline form (ie, ice, crank, or crystal) is a popular drug in this class. It can be ingested orally, smoked, insufflated nasally, or injected intravenously.

An amphetamine-like drug, 3,4-methylenedioxymethamphetamine is a designer drug associated with “rave” parties. Commonly known as ecstasy, XTC, E, and MDMA, it acts as a stimulant and hallucinogen. It increases serotonin release and inhibits serotonin reuptake in the brain. Bruxism and jaw clenching are clues to use of ecstasy. Complications are usually a result of drug effects and nonstop physical activity. Hyponatremia and liver injury progressing to fulminant failure have been reported.

Management of amphetamine intoxication is primarily supportive. Gastric lavage has little role, as absorption following oral ingestion is usually complete at the time of presentation. A careful assessment for complications should be made, including measuring core temperature, obtaining an ECG, and evaluating laboratory data for evidence of renal dysfunction and rhabdomyolysis. Benzodiazepines, often in high dosage, are useful for control of agitation.

Anesthetics (Local and Topical)

Benzocaine, lidocaine, and prilocaine are local anesthetics commonly used during bronchoscopy, endoscopy, oropharyngeal procedures, and transesophageal echocardiography. The most commonly reported toxic effect of local anesthetics is methemoglobinemia (MetHb). Acquired MetHb is caused by the oxidation of ferrous to ferric iron, which reduces the oxygen-carrying capacity of hemoglobin and leads to a functional anemia. A leftward shift of the oxyhemoglobin dissociation curve contributes to tissue hypoxia. An arterial oxygen saturation measured by pulse oximetry that is lower than the calculated oxygen saturation of an ABG is a clue to the presence of MetHb. The arterial blood sample will have a normal PaO_2. Symptoms of MetHb are usually seen at methemoglobin concentrations greater than 10% and include arrhythmias, confusion, cyanosis, disorientation, dizziness, dyspnea, headache, lethargy, and seizure. Vascular and respiratory collapse, coma, and death can occur if MetHb is not treated promptly or with methemoglobin concentrations greater than 50%. Other causes of acquired MetHb to consider include dapsone, organic nitrates (ie, nitric oxide, nitroprusside), rasburicase, and sulfonamide antibiotics. The antidote for acquired MetHb is methylene blue at 1 to 2 mg/kg IV or 100 to 300 mg orally, which causes an enzymatic reduction of methemoglobin to hemoglobin. ILE therapy may be considered in severe or refractory cases.

Benzodiazepines

Benzodiazepine overdose results in a sedative-hypnotic toxidrome (**Table 3**). Activated charcoal may be considered for recent ingestions, and supportive care with intubation may be needed in patients with significant toxicity. Flumazenil is a benzodiazepine receptor antagonist but should not be routinely used. Resedation is likely given the short terminal half-life of flumazenil (42-78 minutes) compared with benzodiazepines. Flumazenil is contraindicated in suspected concurrent cyclic antidepressant overdoses and in patients physically dependent on benzodiazepines due to the risk of seizures. If seizures occur with use of flumazenil, high doses of benzodiazepines may be effective.

β-Blockers

β-Adrenergic blockers produce adverse effects primarily through bradycardia and hypotension. CNS depression may occur with agents such as propranolol, timolol, metoprolol, and acebutolol. Hypotension often results from negative inotropic effects rather than bradycardia. Glucagon is the antidote of choice, because it produces chronotropic and inotropic effects and does not require β-receptors for activity. An initial dose of 2 to 5 mg of glucagon is given intravenously; an infusion of 2 to 10 mg/h can be initiated and then tapered over 12 hours. The goal of treatment is improvement in blood pressure and perfusion rather than an increase in heart rate. Calcium chloride 1 to 3 g IV may be effective in reversing hypotension. In some cases, high-dose insulin therapy (insulin 0.1-10 U/kg/h and glucose 10-75 g/h) may be beneficial. Additional drugs that have had variable efficacy in β-blocker overdoses include atropine, epinephrine, isoproterenol, and dopamine. Transcutaneous pacing and transvenous pacing can be considered in refractory cases. Phosphodiesterase inhibitors such as milrinone, intra-aortic balloon pump, or cardiopulmonary bypass can be considered if the patient does not respond to other interventions.

Calcium-Channel Blockers

Calcium-channel blocker overdose should be considered in hypotensive, bradycardic patients, particularly those with a history of hypertension. In the presence of hemodynamic instability, initial treatment is 1 g of calcium chloride IV. Higher doses of calcium and a continuous infusion (20-50 mg/kg/h) may be required, accompanied by monitoring of ionized calcium levels. High-dose insulin therapy has been effective in severe poisonings. As in β-blocker overdose, glucagon and transcutaneous or transvenous pacing may have beneficial effects.

Carbon Monoxide

Carbon monoxide is a colorless, odorless gas with greater affinity for hemoglobin than oxygen. Carboxyhemoglobin reduces oxygen-carrying capacity and shifts the oxyhemoglobin dissociation curve to the left. The symptoms of carbon monoxide poisoning are nonspecific, with common findings of headache, dizziness, and nausea; severe exposure can result in chest pain, disorientation, seizures, coma, dyspnea, weakness, arrhythmias, and hypotension. Although an increased arterial or venous carboxyhemoglobin level confirms the diagnosis of carbon monoxide poisoning, decisions for aggressive therapy with 100% oxygen should be based primarily on a clinical history suggestive of exposure. High-flow oxygen or intubation with administration of 100% oxygen should be initiated as soon as possible while confirmatory tests are obtained. An ECG, chest radiograph, and ABG measurement should be obtained to assess the severity of toxicity. The finding of metabolic acidosis implies clinically relevant exposure with inadequate oxygen availability at the tissue level. The use of hyperbaric oxygen can be considered for patients with depressed level of consciousness, loss of consciousness, neurological findings other than headache, cardiac instability, carboxyhemoglobin level greater than 25%, or persistent symptoms after normobaric oxygen treatment for 4 to 6 hours.

Cocaine

Cocaine morbidity and mortality are associated with all routes of use, including nasal insufflation, smoking, and IV and oral routes. Toxicities include intracranial hemorrhage (subarachnoid and intraparenchymal), cerebrovascular accidents, seizures, noncardiogenic pulmonary edema, arrhythmias, hypertension, myocardial ischemia, barotrauma, bowel ischemia, hyperthermia, and rhabdomyolysis. Chest pain thought to be ischemic usually responds to nitroglycerin or benzodiazepines, and aspirin should be administered. Phentolamine and calcium-channel blockers are considered second-line agents for chest pain but are rarely needed. Because of hypertension and potential coronary artery vasoconstriction caused by unopposed α-adrenergic activity, it is appropriate to avoid administration of β-1 selective β-blockers in patients manifesting acute sympathomimetic findings. However, the benefits of these agents should be considered in patients with ongoing myocardial ischemia. In the case of severe hypertension, labetalol IV may be the drug of choice because it has both α-adrenergic-blocking and β-adrenergic-blocking properties. High environmental temperatures and increased physical activity increase the

occurrence of rhabdomyolysis; therefore, IV fluid hydration should be instituted until rhabdomyolysis can be excluded.

Cyanide

Cyanide exposure is rare but can occur in occupational settings involving metal extraction, electroplating, chemical synthesis, and firefighting. Cyanide inhibits cytochrome oxidase, which halts oxidative phosphorylation and energy production. Metabolic (lactic) acidosis and decreased oxygen consumption result. Symptoms include nausea and vomiting, agitation, and tachycardia. Serious poisonings result in seizures, coma, apnea, hypotension, arrhythmias, rhabdomyolysis, hepatic necrosis, and acute respiratory distress syndrome. A cyanide antidote kit containing amyl nitrite pearls and 3% sodium nitrite IV can be used to induce formation of methemoglobin, which has a higher affinity for cyanide than cytochrome oxidase. The kit also contains 25% sodium thiosulfate IV, which enhances cyanide conversion to thiocyanate, which is excreted by the kidneys. Hydroxocobalamin has also been used for cyanide poisoning and relies on the formation of nontoxic cyanocobalamin (vitamin B_{12}).

Cyclic Antidepressants

Significant overdoses with cyclic antidepressants present with cardiovascular and CNS manifestations. Cardiovascular toxicities include intraventricular conduction delays, wide complex arrhythmias, and prolonged QRS or QT intervals. Patients may also experience hypoventilation, hypoxemia, hyperthermia, urinary retention, and blurred vision. Altered mental status may be the best predictor of a substantial ingestion, with additional manifestations of delirium, seizures, and coma. Life-threatening events usually occur within the first 6 hours of ingestion. Qualitative urine toxicology or serum levels may confirm the presence of cyclic antidepressants, but serum levels do not correlate with toxicity.

Supportive care for respiratory and cardiovascular toxicities is essential. Activated charcoal administration may be considered if the patient presents within 1 hour of ingestion. Sodium bicarbonate 1 to 2 mEq/kg can be used to alkalinize the blood to a pH of 7.45 to 7.55 and provide a sodium load for prolonged QRS or wide complex arrhythmias. Hypertonic saline may be considered as well as ILE for patients refractory to sodium bicarbonate. Additional treatment may include magnesium IV for torsades de pointes,

benzodiazepines for seizures, and vasopressors (norepinephrine or phenylephrine) for hypotension.

γ-Hydroxybutyrate

γ-Hydroxybutyrate is an illegal substance that is a naturally occurring metabolite of γ-aminobutyric acid. Clinical effects of γ-hydroxybutyrate ingestion include hypothermia, loss of consciousness, coma, respiratory depression, seizure-like activity, bradycardia, hypotension, and death. Concomitant use of alcohol results in synergistic CNS and respiratory effects. Similar manifestations occur with abuse of related agents such as γ-butyrolactone, 1,4-butanediol, and γ-hydroxyvalerate. Activated charcoal is unlikely to be of benefit because of the rapid absorption of these substances. Although patients usually recover spontaneously in hours to days, supportive therapy with airway protection and mechanical ventilation may be necessary. Use of physostigmine to reverse CNS effects is not recommended.

Lithium

Although arrhythmias are reported, CNS abnormalities (lethargy, dysarthria, delirium, seizures, and coma) are the major manifestation of lithium toxicity. Symptoms of GI distress, polyuria, and polydipsia may be present. Patients who chronically ingest lithium are more prone to toxic effects. Lithium levels should be measured at presentation and 2 hours later to assess for increasing concentration. Whole bowel irrigation may be considered in serious toxicity and for sustained-release formulations because lithium is not adsorbed by charcoal. Saline infusions are used to maintain adequate urine output and should target serum sodium levels of 140 to 145 mEq/L as lithium clearance is reduced in hyponatremia. Diuretics can worsen toxicity and should be avoided. Hemodialysis is indicated in life-threatening toxicity, including severe neurological dysfunction, volume overload, or levels greater than 4 mmol/L in acute ingestion or greater than 2.5 mmol/L in chronic ingestions. Redistribution between intracellular and extracellular compartments may cause a rebound increase in lithium levels within 8 hours after dialysis; therefore, levels should be rechecked 12 hours after dialysis. Sodium polystyrene sulfonate has been suggested to decrease lithium absorption, but evidence of clinical benefit is lacking.

Narcotics

Overdose deaths related to prescription and illicit narcotic use continue to increase, specifically deaths related to heroin. Overdose symptoms include altered mental status, respiratory depression, and miosis. However, miosis is not seen with meperidine or tramadol toxicity. Additional clinical findings include hypotension, pulmonary edema, bronchospasm (heroin), seizures (meperidine), ileus, nausea, vomiting, and pruritus. Naloxone, an opioid receptor antagonist, is dosed initially at 0.4 to 2 mg, with doses repeated every 2 to 3 minutes as required. Doses as high as 20 mg may be required to reverse the effects of codeine, pentazocine, methadone, oxycodone, hydrocodone, and fentanyl. The IV route is preferred, but naloxone can be administered by intramuscular, sublingual, intranasal, or endotracheal routes. Due to the short half-life of naloxone, continuous infusions may be necessary at hourly doses of one-half to two-thirds of the amount in milligrams that was needed to initially reverse the respiratory depression. Noncardiogenic pulmonary edema can occur with narcotic overdose and is managed with supportive care.

Organophosphates, Carbamates, and Nerve Gas

Organophosphate and carbamate poisoning producing a cholinergic syndrome is more common in developing countries than in the United States. Some nerve gases (sarin) used in terrorist attacks produce similar toxicities. Cholinergic poisoning exerts potential deleterious effects on 3 systems: (1) the muscarinic (parasympathetic) system, causing bronchorrhea, bradycardia, and SLUDGE syndrome (**Table 3**); (2) the nicotinic autonomic system, resulting in muscle weakness; and (3) the CNS, including confusion, slurred speech, and central respiratory depression. Bronchorrhea, bronchospasm, and respiratory depression are the most significant toxicities. Both atropine and pralidoxime IV are indicated. If no CNS symptoms are present, glycopyrrolate can be substituted for atropine. Atropine is dosed at 2 to 4 mg with repeated doses every 2 to 5 minutes or by continuous infusion, but it does not reverse nicotinic manifestations; therefore, patients with substantial respiratory muscle weakness require the use of pralidoxime (1-2 g with repeated doses every 10-12 hours). An intermediate syndrome of respiratory paralysis, bulbar weakness, proximal limb weakness, and decreased reflexes may develop 24 to 96 hours after resolution of the cholinergic crisis.

Propofol

Propofol infusion syndrome (PRIS) is manifested by symptoms including

refractory bradycardia, lactic acidosis, rhabdomyolysis, renal failure, and hyperlipidemia. This syndrome is usually associated with doses of propofol greater than 4 mg/kg/h for longer than 48 hours. However, metabolic acidosis has been reported within 1 to 4 hours after the initiation of propofol infusion. Predisposing factors associated with PRIS include young age, CNS or respiratory illness, endogenous catecholamines, glucocorticoids, systemic inflammation, inadequate carbohydrate intake, and subclinical mitochondrial disease.

PRIS can be prevented by early adequate carbohydrate intake to decrease the mobilization of fat stores and fat metabolism and to decrease the circulating fatty acid load. Prompt recognition of early signs of PRIS (elevated serum lactate, creatine kinase, and myoglobin level or hyperlipidemia) is essential for successful recovery. Management of PRIS includes discontinuation of propofol and use of alternative sedative agents. The most effective treatment for severe PRIS is cardiorespiratory support and hemodialysis or hemofiltration.

Salicylates

Symptoms of salicylate poisoning may include tinnitus, depressed level of consciousness, fever, anion-gap metabolic acidosis, coagulopathy, prolonged prothrombin time, transient hepatotoxicity, and noncardiogenic pulmonary edema. The Done nomogram, used to estimate the severity of an acute salicylate overdose, may not reliably correlate with observed toxicity. Gastric lavage may be considered for substantial ingestions, and activated charcoal should be administered within 1 hour of ingestion. Alkalinization of the urine with sodium bicarbonate IV is indicated to enhance salicylate excretion if serum levels are greater than 35 mg/dL. Hemodialysis may be indicated with levels greater than 100 mg/dL, refractory seizures, persistent alteration in mental status, or refractory acidosis.

Selective Serotonin Reuptake Inhibitors

Toxicity with selective serotonin reuptake inhibitors (SSRIs) is less severe than toxicity with cyclic antidepressants. Acute overdoses of SSRIs can result in nausea, dizziness, CNS depression, and arrhythmias. Serotonin syndrome, a potentially life-threatening condition, can be seen with therapeutic doses of SSRIs, with overdoses of SSRIs, or with SSRIs in combination with other proserotonergic agents such as monoamine oxidase inhibitors, cyclic antidepressants, lithium, opioids (meperidine, tramadol, dextromethorphan, and

pentazocine), amphetamine, serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), trazodone, and drugs that inhibit hepatic cytochrome P450. Clinical manifestations include agitation, coma, blood pressure fluctuations, hyperthermia, tachycardia, diaphoresis, diarrhea, tremor, rigidity, myoclonus, and seizures. Management includes activated charcoal if the patient presents within 1 hour of ingestion, sodium bicarbonate for cardiac toxicities, cooling, anticonvulsants, and benzodiazepines for agitation and muscle rigidity. Cyproheptadine, a serotonin antagonist, has been used as a treatment option despite lack of known benefit. The use of bromocriptine or dantrolene has no role in treatment of SSRI poisoning. Most cases resolve in 24 to 72 hours.

Sulfonylureas

Poisoning with sulfonylureas can produce persistent hypoglycemia refractory to IV concentrated glucose. Sulfonylureas stimulate the release of insulin from the pancreas, as does concentrated glucose administration. Octreotide, a synthetic analog of somatostatin, has been used effectively for sulfonylurea toxicity because this agent inhibits insulin secretion, thereby increasing serum glucose, decreasing concentrated glucose requirements, and decreasing recurrent hypoglycemic events compared with IV glucose alone. Optimal doses of octreotide have not been established as its use is off-label. Case reports suggest using doses of 50 to 450 μg subcutaneous or IV in divided doses or as a continuous infusion.

Synthetic Legal Intoxicating Drugs

The use of synthetic legal intoxicating drugs is on the rise. Many individual synthetic drugs are now illegal, but new drugs and chemicals are being created for alternative uses. These drugs are not detected on qualitative urine toxicology tests. Physical examination, symptoms, and synthetic drug use history are essential in establishing the diagnosis. Bath salts, which contain derivatives of cathinones, are orally ingested, injected, or nasally insufflated. They cause a sympathomimetic toxidrome (**Table 3**) with delusions, hallucinations, bruxism, erratic behaviors, or hyperthermia with clinical effects lasting greater than 24 hours. Synthetic cannabinoids, often sold as herbal incense that are inhaled or smoked, are full agonists of cannabinoid receptors and have a greater risk for overdose and toxicity compared with marijuana. Serious adverse effects of synthetic cannabinoids include psychosis, arrhythmias, myocardial ischemia, renal failure, stroke, and seizures. Management of toxicity from synthetic legal

intoxicating drugs is mainly supportive and includes the use of benzodiazepines for agitation.

Herbal Medicine and Dietary Supplements

Herbal medicines are not required to undergo safety or efficacy testing in the United States. Poisoning can result from contamination of the product, misuse, or interaction with other medications. Aconitine and cardiac glycosides are common ingredients in Asian herbal medications and can result in paresthesias, hypersalivation, visual disturbances, dizziness, nausea, vomiting, diarrhea, muscle weakness, sinus bradycardia, and ventricular arrhythmias. Atropine can be considered for bradycardia or hypersalivation. A digoxin level should be obtained but may not correlate with clinical findings, because numerous cardiac glycosides will not cross-react in the digoxin immunoassay. With substantial toxicity, digoxin-specific antibodies should be administered.

CNS stimulation and a sympathomimetic syndrome are characteristic of preparations containing ephedrine and pseudoephedrine, which are often found in products marketed as herbal ecstasy. Stroke, myocardial infarction, arrhythmias, liver failure, and death have been reported. Ephedra-free products have been associated with cardiovascular toxicity. Supportive care similar to management of other sympathomimetic syndromes is indicated.

Ginkgo biloba has been reported to result in spontaneous bleeding, including subdural hematomas due to antiplatelet-activating factor effects. Garlic, feverfew, and ginseng can result in bleeding due to inhibition of platelet aggregation, and ginseng has been associated with hypoglycemia. Contaminants found in some products, such as mercury, arsenic, lead, and antihistamines, can cause toxicities.

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CHAPTER 41

Hypothermia, Hyperthermia, and Near Drowning

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Key words: heatstroke, hyperthermia, hypothermia, malignant hyperthermia, neuroleptic malignant syndrome, near drowning, drowning, submersion injury

TEMPERATURE REGULATION

The balance between heat production and heat loss normally maintains the core body temperature at 36.6°C ± 0.38°C (97.9°F ± 0.7°F). At rest, the trunk viscera (primarily heart and liver) supply 56% of heat; during exercise, muscle activity may account for 90% of heat generation. Heat production increases with shivering and with exercise. Most heat loss (50%-70%) normally occurs from the skin and lungs through radiation in neutral environments. Conduction of heat through direct contact with cooler objects or loss of heat due to convection accounts for a smaller percentage of heat loss. Evaporation of sweat from the skin is the major mechanism of heat loss in a warm environment.

The anterior hypothalamus is responsible for temperature perception and initiation of physiological responses. When a temperature increase is perceived, hypothalamic modulation results in increased sweating (a cholinergically mediated response), cutaneous vasodilation, and decreased muscle tone. Conversely, a temperature decrease results in inhibition of sweating, cutaneous vasoconstriction, increased muscle tone, and shivering. These homeostatic temperature mechanisms deteriorate with age.

HYPOTHERMIA

Definitions and Causes

Hypothermia is defined as a core body temperature of less than 35°C (95°F). Multiple factors can lead to increased heat loss, decreased heat production, or impaired thermoregulation (**Table 1**). Hypothermia may be characterized as primary (accidental), due to exposure to cold temperatures, or secondary, resulting from an underlying disorder such as myxedema. Exposure along with underlying chronic diseases or impairment from ethanol, drugs, or mental illness is frequently found in hypothermic patients. Immersion hypothermia is often distinguished from nonimmersion hypothermia because immersion hypothermia occurs more rapidly and is more often associated with asphyxia. Hypothermia is frequently noted in trauma patients and is associated with increased mortality rates.

Table 1. Factors Predisposing to Hypothermia

Increased heat loss	Decreased heat production	Impaired thermoregulation	Miscellaneous states
Environmental exposure Skin disorders Burns Dermatitis Psoriasis Vasodilation Alcohol Drugs (phenothiazines) Iatrogenic Heatstroke treatment Environmental cold (operating suite)	Endocrine disorders Hypopituitarism Hypothyroidism Hypoadrenalism Insufficient fuel Hypoglycemia Anorexia nervosa Malnutrition Extreme exertion Neuromuscular inefficiency Extremes of age Inactivity Impaired shivering	Peripheral dysfunction Neuropathies Spinal cord transection Diabetes Central dysfunction Central nervous system hemorrhage or trauma Cerebrovascular accident Neoplasm Parkinson disease Anorexia nervosa Drugs Cyclic antidepressants Narcotics Sedatives Alcohols	Sepsis Pancreatitis Carcinomatosis Uremia Sarcoidosis

To anticipate physiological changes and facilitate management, hypothermia can be classified by the degree of temperature reduction (**Table 2**). The classification for trauma patients is more conservative.

Table 2. Classification of Hypothermia

Degree of Hypothermia	Usual Classification, °C (°F)	Trauma Classification, °C (°F)
Mild	32-35 (90-95)	34-36 (93-97)
Moderate	28-32 (82-90)	32-34 (90-93)

Severe	<28 (<82)	<32 (<90)

Pathophysiological Changes

General Metabolic Changes

Hypothermia produces multisystemic involvement that varies with core temperature (**Table 3**). The initial response to cold is cutaneous vasoconstriction, which results in shunting of blood from extremities to the body core. Vasodilation secondary to ethanol or other drugs can compromise this normal compensatory vasoconstriction. Vasoconstriction fails at temperatures less than 24°C (75°F), and the rate of heat loss increases because of relative vasodilation.

Heat production is increased by the onset of shivering with core temperatures of 30°C to 35°C (86°F-95°F). Shivering continues until glycogen stores are depleted, which usually occurs when the body temperature reaches 30°C (86°F).

Table 3. Manifestations of Hypothermia

Degree of Hyperthermia Core Temperature, °C (°F)	**Musculosketal Signs**	**Neurological Signs**
Mild		
36 (96.7)	Shivering begins	Slurred speech
34 (93.2)	Maximal shivering	Increased confusion
33 (91.4)	Decreased shivering	Stupor
Moderate		
32 (89.6)	Shivering nearly absent; onset of muscle rigidity	Pupils dilated
30 (86)	—	Deep tendon reflexes absent
28 (82.4)	Extreme muscle rigidity	No voluntary movement
Severe		
24 (75.2)	Patient appears dead	—
18-20 (64.4-68)	—	Isoelectric

		electroencephalogram

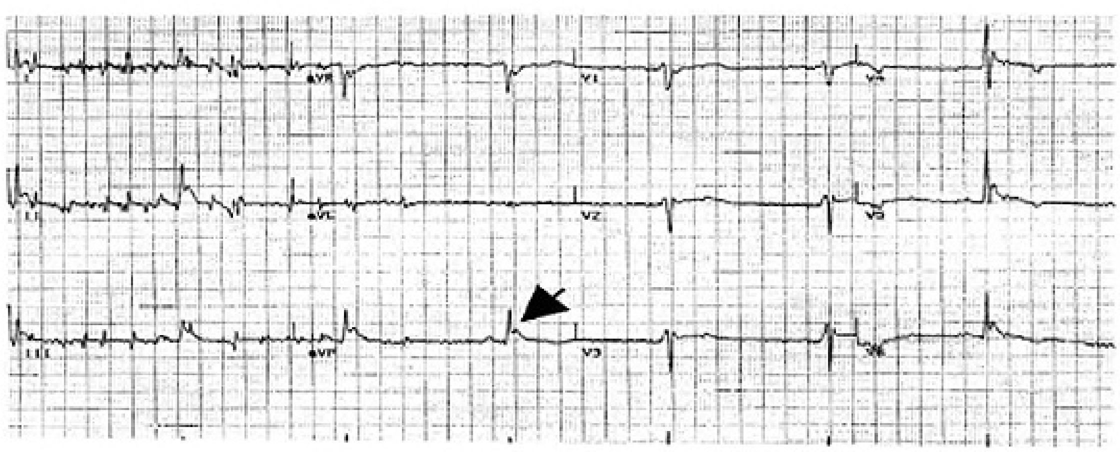
Cardiovascular System

An initial tachycardia is followed by progressive bradycardia. The pulse rate decreases by 50% when core temperature reaches 28°C (82°F). Cardiac function and blood pressure also decline proportionately as the core temperature decreases. Systemic vascular resistance predictably increases.

Hypothermia produces a variety of myocardial conduction abnormalities. Atrial fibrillation is common and usually converts to sinus rhythm spontaneously during rewarming. At temperatures of less than 29°C (84°F), ventricular fibrillation can occur spontaneously or be induced by movement or invasive procedures. Asystole usually occurs at temperatures less than 20°C (68°F). Ventricular fibrillation and other arrhythmias are usually refractory to defibrillation and drug treatment until the core temperature increases to approximately 30°C (86°F).

The most characteristic electrocardiographic abnormality of hypothermia is the J wave (also called the Osborn wave) at the junction of the QRS complex and ST segment (**Figure 1**). The J wave can occur in patients with core temperatures of less than 32°C (90°F). The J wave is not pathognomonic or specific for hypothermia and does not have prognostic value. J waves must be differentiated from ST-segment elevation that indicates myocardial infarction. Prolongation of the PR, QRS, and QT intervals may be noted.

Figure 1. Electrocardiogram of hypothermic patient showing J wave (arrow)



Other Organ Systems

As temperature decreases, tidal volume and respiratory rate will decrease. The cough reflex may be blunted, and cold-induced bronchorrhea may contribute to atelectasis. Hypoxemia may develop early depending on the circumstances (eg, water immersion, aspiration). Although renal blood flow and glomerular filtration rate decrease in hypothermia, an initial cold-induced diuresis occurs due to the relative central hypervolemia resulting from peripheral vasoconstriction. Additional contributory factors include the inhibition of antidiuretic hormone release and renal tubular concentrating defects. Ethanol exacerbates the diuresis. With warming, volume depletion often becomes evident.

With mild hypothermia, patients may exhibit confusion, lethargy, or combativeness. Below a core temperature of 32°C (90°F), the patient is usually unconscious with impaired brain stem function. Pupils dilate below a core temperature of 30°C (86°F). Intestinal motility decreases at less than 34°C (93°F), resulting in the common finding of ileus. Hepatic dysfunction affects glucose production as well as drug metabolism.

Laboratory Findings

The physiological changes described are reflected by laboratory tests. An increased hematocrit is usually found, with normal or low platelet and white blood cell counts. The increase in hematocrit is due to hemoconcentration and splenic contraction. However, restoration of intravascular volume and warming often result in a mild anemia. Platelet dysfunction occurs with hypothermia and may compromise hemostasis, especially in the trauma patient. Although disseminated intravascular coagulation often develops, initial coagulation studies may be normal because these laboratory measurements are performed on warmed blood. Electrolytes are variable, and increased values of serum urea nitrogen and creatinine result from hypovolemia. Hyperglycemia is common and attributable to catecholamine-induced glycogenolysis, decreased insulin release, and inhibition of insulin transport. Hypoglycemia may be found in malnourished and alcoholic patients and patients with depletion of glycogen stores. The most common acid-base abnormalities in hypothermia are respiratory and metabolic acidoses. There is general agreement that arterial blood gas values do not need to be corrected for temperature. Uncorrected values can be compared and interpreted in relation to normal values at 37°C (98.6°F).

Diagnosis

The clinical presentation of hypothermia varies with the cause, rapidity of cooling, severity, and duration. The clinical suspicion of hypothermia should be confirmed with an accurate core temperature measurement. Any low temperature (35°C [95°F]) should be checked with a thermometer capable of registering lower temperatures. Bladder catheters with thermistors provide readings similar to those provided by intravascular devices. A rectal probe may be most practical even though measurements may lag behind core changes. The probe should be inserted to an adequate depth (approximately 15 cm), avoiding cold fecal material. An esophageal probe is an alternative, but readings may be falsely elevated in an intubated patient receiving heated oxygen. Reliability of tympanic temperature devices has not been established in hypothermia.

Hospital Management

The severity of hypothermia, clinical findings, and comorbid conditions of the patient determine the aggressiveness of resuscitation techniques. The following measures, along with rewarming interventions, should be instituted as indicated.

- *Airway management:* Intubation is often necessary for airway protection and/or delivery of supplemental oxygen or heated oxygen. The orotracheal route is preferred given the risk of traumatic bleeding with the nasal route. However, muscle rigidity may preclude mouth opening. Neuromuscular blockers are not likely to be effective at temperatures less than 30°C (86°F). Blind nasotracheal intubation may be facilitated by use of a smaller endotracheal tube and topical vasoconstrictors. Endotracheal tube cuff pressures should be monitored after rewarming because volume and pressure will increase.

- *Supplemental oxygen:* High oxygen concentrations should be used until an arterial blood gas is obtained. Pulse oximetry is not reliable as a guide to therapy in the setting of moderate to severe hypothermia and hypoperfusion.

- *Cardiopulmonary resuscitation:* Chest compressions should be initiated if the patient is pulseless (assess for 30-45 seconds) or has a nonperfusing rhythm. Chest wall compression is often difficult, and personnel must be relieved regularly to avoid fatigue.

- *Electrocardiogram monitoring:* (1) Bradycardia: Pharmacological manipulation and pacing should be avoided. (2) Ventricular fibrillation:

Initial defibrillation should be attempted even if the temperature is less than 30°C (86°F). If defibrillation is unsuccessful, rewarming should be instituted. Defibrillation can be attempted after every 1°C to 2°C (2°F-3.6°F) increase in temperature or when the core temperature reaches 30°C to 32°C (86°F-90°F). IV drugs should be avoided until the temperature increases to approximately 30°C, and then the lowest effective dose should be used. Dosing intervals should be increased in hypothermic patients because of altered hepatic and renal metabolism. Amiodarone is a reasonable initial antiarrhythmic drug. Magnesium sulfate has also been used successfully. (3) Asystole: Advanced life support guidelines should be followed, and pharmacological agents should be administered when the temperature approaches 30°C.

- *IV fluids:* All patients require fluids for hypovolemia. Warm normal saline containing glucose is a reasonable choice. Increased fluid quantities are often necessary during rewarming to prevent or treat hypotension as vasoconstriction is reversed. Lactated Ringer's solution should be avoided given the potential for impaired hepatic metabolism of lactate.

- *Vasopressor drugs:* Hemodynamic instability should first be addressed with volume replacement. Vasopressor drugs have a minimal effect on constricted vessels and increase the risk of dysrhythmias.

- *Nasogastric or orogastric tube:* A tube is inserted to relieve or prevent gastric distention.

- *Urinary catheter:* A catheter is inserted to monitor urine output.

- *Venous access:* Peripheral venous catheters are preferred. Central venous lines (subclavian, internal jugular) are not routinely recommended because they can precipitate dysrhythmias or lead to perforation of cold vessels.

- *Laboratory studies:* Studies should include complete blood count, prothrombin time, partial thromboplastin time, electrolytes, creatine kinase level, and arterial blood gases. Thyroid function evaluation, toxicology screen, and blood cultures should be obtained as warranted.

- *Associated conditions:* The clinician should assess the patient for conditions requiring urgent intervention, such as hypoglycemia, sepsis, adrenal insufficiency, and hypothyroidism.

Rewarming Methods

Although warming is the primary treatment for hypothermia, controversy exists as to the optimal method, duration, and rate of rewarming. Rapid rewarming does not necessarily lead to improved survival. No controlled studies comparing rewarming methods are available, and rigid treatment protocols cannot be recommended. Three types of rewarming techniques exist: passive external rewarming (PER), active external rewarming (AER), and active core rewarming (ACR). The clinical circumstances of the patient (severity of exposure, comorbidities, hemodynamic status), availability of resources, and advantages and disadvantages of the various techniques should be taken into account when a rewarming plan is developed.

PER is the least invasive and slowest method. It involves placing the patient in a warm environment, providing warm clothing or blankets, and allowing the body to regain heat. This technique should be applied as the sole method only in patients with mild hypothermia. The patient must be able to generate heat for PER to be effective. Rewarming rates with PER in mild hypothermia vary between 0.5°C/h and 2.0°C/h (1°F/h and 3.6°F/h).

AER involves the external application of heat, such as warming blankets, heating pads, radiant heat lamps, or immersion in warm water. Forced air warming devices are the most effective and practical means of applying AER, particularly in the perioperative period. The rate of rewarming is approximately 2.5°C/h (4.5°F/h), and patients with a smaller body surface area warm faster. The advantages of AER are its ease of institution, ready availability, low cost, and noninvasiveness.

ACR is the most rapid and most invasive method; it involves the application of heat to the body core. Active core rewarming is indicated in patients with a core temperature of less than 28°C (82°F) or with a nonperfusing rhythm. Techniques for ACR range from simple to complex and include heated humidified oxygen; heated IV fluids; thoracic lavage; peritoneal lavage; gastric, bladder, or rectal lavage; hemodialysis; continuous venovenous rewarming; cardiopulmonary bypass; and extracorporeal membrane oxygenation (ECMO).

One of the simplest ACR methods to institute entails warm, humidified, inhaled oxygen (42°C-45°C [107.6°F-113°F]), which prevents further respiratory heat loss and may result in a modest heat gain. A rewarming rate of 1°C/h to 2.5°C/h (2°F/h-4.5°F/h) can be expected. This technique should be used on most patients with moderate to severe hypothermia. Heated IV fluids (40°C-42°C [104°F-

107.6°F]) are easy to administer, and transfused blood should also be warmed. Short lengths of tubing should be used to minimize heat loss to the environment. Although gastric, bladder, or rectal lavage with warm fluids is a simple procedure, little information is available to suggest efficacy. Heat transfer by conduction is minimal because of the limited available surface area. Gastric lavage cannot be instituted during chest compressions and may predispose to aspiration. This method should generally be used only as an adjunct until more invasive rewarming methods can be initiated.

For patients with severe hypothermia, more invasive ACR is preferred: peritoneal lavage, thoracic lavage, hemodialysis, continuous venovenous rewarming, cardiopulmonary bypass, and ECMO. These procedures require specialized equipment and intensive care. However, they can be efficient at rewarming and, in the case of cardiopulmonary bypass, may provide for hemodynamic stabilization of the patient. Peritoneal lavage can be instituted by using dialysate heated to 40°C to 45°C (104°F-113°F). Closed thoracic lavage involves placement of anterior and posterior chest tubes, infusion of heated saline or sterile water (40°C-42°C [104°F-107.6°F]) through the anterior tube, and gravity drainage from the posterior tube. Hemodialysis, using a 2-way-flow catheter, may be best suited for the patient who is hemodynamically stable. It may also be preferred when severe renal dysfunction or certain intoxications are present. Continuous venovenous rewarming uses a modified fluid warmer with 40°C (104°F) water infused through the inner chamber. Cardiopulmonary bypass (femoral-femoral or atrial-aortic) is the most invasive and labor-intensive technique for rewarming. It has the advantage of providing complete hemodynamic support, restoring organ perfusion, and offering rapid rewarming rates (1°C-2°C every 3-5 minutes). Venovenous ECMO has been used recently for treatment of severe hypothermia in patients with cardiovascular instability. Advantages include the availability of portable units, limited need for heparinization, percutaneous cannulation that does not interfere with resuscitation, support of pulmonary function, and rewarming rates similar to cardiopulmonary bypass.

Rewarming may combine multiple techniques, such as AER with ACR, using heated oxygen and IV fluids. In all cases, complications of rewarming must be anticipated, such as disseminated intravascular coagulation, pulmonary edema, compartment syndromes, rhabdomyolysis, and acute tubular necrosis.

Outcome From Hypothermia

There are no strong predictors of death or permanent neurological dysfunction in severe hypothermia. Thus, no definitive indicators are available to suggest which patients can or cannot be resuscitated successfully. Core temperature before rewarming and time to rewarming are not predictive of outcome. Patients with a core temperature as low as 13.7°C (56.6°F) have survived with intact neurological function. Severe hyperkalemia (>10 mEq/L) may be a marker of death. In general, resuscitative efforts should continue until core temperature is 32°C (90°F). However, the decision to terminate resuscitation must be individualized to the circumstances.

HYPERTHERMIA

Definition

Heatstroke is a life-threatening medical emergency that occurs when homeostatic thermoregulatory mechanisms fail. This failure usually results in elevation of body temperature to more than 41°C (105.8°F), producing multisystemic organ dysfunction. Two syndromes of heatstroke occur: classic nonexertional heatstroke and exertional heatstroke. Classic heatstroke typically affects elderly individuals with underlying chronic illness. The occurrence of classic heatstroke is often predictable when heat waves occur. The syndrome usually develops over several days and results in marked dehydration and anhidrosis. Exertional heatstroke typically occurs in young healthy individuals such as athletes and military recruits exercising in hot environments. This syndrome occurs sporadically and often unpredictably. Dehydration is less severe, and approximately 50% of individuals will have profuse sweating.

Predisposing Factors

Heatstroke results from increased heat production and/or decreased heat loss (**Table 4**). Environmental factors of high heat and humidity contribute to heat production and limit heat loss. As ambient temperature approaches body temperature, evaporation of sweat becomes the primary cooling mechanism. However, conditions of high humidity (>75%) limit the evaporation of sweat and loss of heat from the body. Sympathomimetic drugs, such as cocaine, amphetamines, phencyclidine, and ephedrine, increase muscle activity and can disrupt hypothalamic regulatory mechanisms. Drugs with anticholinergic effects, such as cyclic antidepressants, antihistamines, and antipsychotics, inhibit cholinergically mediated heat-induced sweating and disrupt hypothalamic

function. Ethanol can contribute to heatstroke through vasodilation resulting in heat gain, impaired perception of the environment, and diuresis. β-Adrenergic blockers can impair the cardiovascular response of increasing cardiac output as compensation for vasodilation and can decrease cutaneous blood flow.

Table 4. Predisposing Factors for Heatstroke

Increased heat production
Exercise
Fever
Thyrotoxicosis
Hypothalamic dysfunction
Drugs (sympathomimetics)
Environmental heat stress
Decreased heat loss
Environmental heat stress
Cardiac disease
Peripheral vascular disease
Dehydration
Obesity
Skin disease
Anticholinergic drugs
Ethanol
β-Blockers

Diagnosis

The diagnosis of heatstroke requires a history of exposure to a heat load (either internal or external), severe central nervous system (CNS) dysfunction, and elevated temperature (usually >40°C [104°F]). The absolute temperature may not be critical since cooling measures are often instituted before the patient presents to a hospital. The presence of CNS abnormalities distinguishes heatstroke from less severe forms of heat injury such as heat exhaustion. Sweating may or may not be present.

Clinical Manifestations

Symptoms of heatstroke vary with the rapidity of onset, severity and type of exposure (temperature and duration, exertional vs nonexertional), and comorbid conditions. Profound CNS dysfunction is a defining characteristic of heatstroke and may range from bizarre behavior, delirium, and confusion to decerebrate rigidity, cerebellar dysfunction, seizures, and coma. These changes are potentially reversible, although permanent deficits can occur.

Tachycardia, an almost universal finding in heatstroke, occurs in response to peripheral vasodilation and the need for increased cardiac output. The peripheral vascular resistance is usually low unless severe hypovolemia is present. Compensatory vasoconstriction occurs in the splanchnic and renal vascular beds. If the patient is unable to increase cardiac output, hypotension develops. A variety of electrocardiographic changes have been described in heatstroke, including conduction defects, prolonged QT interval, and nonspecific ST-T changes.

Tachypnea may result in a marked respiratory alkalosis. However, patients with exertional heatstroke usually have lactic acidosis. Hypoglycemia may be present in patients with exertional heatstroke because of increased glucose utilization and impaired hepatic gluconeogenesis. Rhabdomyolysis and renal failure occur more commonly with exertional heatstroke and may be due to myoglobinuria, thermal parenchymal damage, or decreased renal blood flow. Hematological effects include leukocytosis and hypocoagulability, which may progress to disseminated intravascular coagulation. Hepatic injury results in cholestasis and elevation of transaminase levels.

Electrolyte concentrations vary in heatstroke. Hyperkalemia can result from rhabdomyolysis, but hypokalemia occurs more commonly. Hypocalcemia can occur, particularly with rhabdomyolysis, but usually does not require therapy.

Differential Diagnosis

The history and physical findings usually indicate the diagnosis of heatstroke. In the absence of adequate history, other processes to be considered include CNS infection, hypothalamic lesions, thyrotoxicosis, and other hyperthermic syndromes.

Treatment

Along with resuscitative measures, immediate cooling should be instituted for any patient with a temperature of greater than 41°C (105.8°F). Two methods of cooling have been used: conductive cooling and evaporative cooling. Because definitive human studies are lacking, the optimal cooling method remains controversial.

Direct cooling by enhancing conduction of heat from the body can be accomplished by immersing the patient in cold water. Skin massage to counter

cutaneous vasoconstriction and shivering in the limbs has been recommended. This method requires considerable staff time and may interfere with other resuscitative measures. Variants of this method include ice-water soaks, ice applied to the entire body, and application of ice packs to the axillae, groin, and neck.

Evaporative cooling is another commonly used cooling method. The unclothed patient is sprayed with warm (not cold) water. Air flow is created with use of fans to enhance evaporative cooling. This method allows personnel to institute other resuscitative measures while cooling occurs.

Other cooling methods, such as peritoneal lavage, iced gastric lavage, or cardiopulmonary bypass, have not been effectively tested in humans. Endovascular cooling in heat stroke has been reported. Antipyretics are not indicated, and dantrolene is ineffective.

In addition to cooling, intubation for airway protection is required in many patients. Supplemental oxygen should be administered to all patients. The type and quantity of IV fluids should be individualized based on assessment of electrolytes and volume status. Overaggressive hydration during cooling may result in cardiac decompensation, especially in elderly patients. Hypotension usually responds to cooling as peripheral vasodilation decreases. Vasopressor agents may result in vasoconstriction and an undesirable decrease in heat exchange. Benzodiazepines should be used to control any seizure activity. A thermistor probe should be used to monitor core temperature during cooling efforts. Cooling should be stopped at 38.0°C to 38.8°C (100.4°F-102°F) to prevent hypothermic overshoot. Continued monitoring is needed to detect a later increase in core temperature.

Outcome

With appropriate management, the survival rate from heatstroke approaches 90%. However, morbidity is related to the duration of hyperthermia and to underlying conditions. Advanced age, hypotension, coagulopathy, hyperkalemia, acute renal failure, and prolonged coma are associated with a poor prognosis. Elevated lactate levels are associated with a poor prognosis in classic heatstroke but not in exertional heatstroke.

MALIGNANT HYPERTHERMIA

Definition

Malignant hyperthermia (MH) is a drug-induced or stress-induced hypermetabolic syndrome characterized by hyperthermia, muscle contractures, and cardiovascular instability. It results from a genetic defect of calcium transport in skeletal muscle. The primary defects are postulated to be impaired reuptake of calcium into the sarcoplasmic reticulum, increased release of calcium from the sarcoplasmic reticulum, and a defect in the calcium mediated coupling contraction mechanism. MH is genetically transmitted as an autosomal dominant trait and occurs in 1 in 50 to 1 in 150,000 adults who receive anesthesia.

Triggers

Halothane and succinylcholine have been involved in the majority of reported cases of MH. Additional potentiating drugs include muscle relaxants, inhalational anesthetic agents, and drugs such as ethanol, caffeine, sympathomimetics, parasympathomimetics, cardiac glycosides, and quinidine analogs. Less commonly, MH can be precipitated by infection, physical or emotional stress, anoxia, or high ambient temperature. Nondepolarizing neuromuscular blockers, etomidate, nitrous oxide, ketamine, opiates, barbiturates, benzodiazepines, propofol, and local anesthetics are considered safe to use in patients with MH.

Clinical Manifestations

Manifestations of MH usually occur within 30 minutes of anesthesia in 90% of patients. However, the syndrome may occur postoperatively. Muscle rigidity begins in the muscles of the extremities or the chest. In patients receiving succinylcholine, stiffness most commonly begins in the jaw. Development of masseter spasm after administration of succinylcholine may be an early sign of possible MH. Tachycardia is another early, although nonspecific, sign.

Monitoring arterial blood gases or end-tidal carbon dioxide may reveal an early increase in carbon dioxide. Hypertension and mottling of the skin also occur. The increase in temperature usually occurs later but is followed rapidly by acidosis, ventricular arrhythmias, and hypotension. Laboratory abnormalities include increased levels of sodium, calcium, magnesium, potassium, phosphate, creatine kinase, and lactate dehydrogenase. Lactate levels are increased, and arterial blood gases indicate hypoxemia and an increase in Pa_{CO_2}.

Treatment

Once the diagnosis of MH is entertained, the inciting drug should be discontinued immediately. The most effective therapy is dantrolene, a drug that prevents release of calcium by the sarcoplasmic reticulum. Uncoupling the excitation-contraction mechanism in skeletal muscle decreases thermogenesis. Dantrolene should be administered by rapid IV push beginning at a dose of 2.5 mg/kg and repeated every 5 minutes until the symptoms subside or the maximum dose of 10 mg/kg has been reached. Decreasing muscle rigidity should be evident within minutes. Subsequent doses of 1 mg/kg every 4 to 6 hours should be continued for 36 to 48 hours. If dantrolene is ineffective or slowly effective, evaporative cooling methods can also be used. Calcium-channel blockers should be avoided.

The Malignant Hyperthermia Association of the United States (www.mhaus.org) provides useful information and a hotline for assistance in managing MH.

NEUROLEPTIC MALIGNANT SYNDROME

Definition

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction, usually to neuroleptic drugs, characterized by hyperthermia, muscle rigidity, alterations in mental status, autonomic dysfunction, and rhabdomyolysis. It may occur in up to 1% of all patients receiving neuroleptic agents and affects men more than women and the young more than the old. The pathogenesis is thought to be related to CNS dopamine antagonism and altered temperature set point in the hypothalamus.

Triggers

Although the majority of cases of NMS have been associated with haloperidol, the following agents have been associated as well: butyrophenones, phenothiazines, thioxanthenes, dopamine-depleting agents, dibenzoxazepines, and withdrawal of levodopa-carbidopa or amantadine. NMS has been reported with the newer atypical antipsychotic agents such as clozapine, risperidone, olanzapine, ziprasidone, aripiprazole, and quetiapine. Rechallenge with an inciting drug may not result in recurrence of NMS.

Clinical Manifestations

NMS usually occurs 1 to 3 days after initiation of a neuroleptic agent or change in the dose, and the syndrome may last for 1 to 3 weeks. Hyperthermia is present, and the average maximal temperature is 39.9°C (103.8°F). However, NMS has been reported to occur without temperature elevation. Autonomic dysfunction includes tachycardia, diaphoresis, blood pressure instability, and arrhythmias. Autonomic dysfunction may precede changes in muscle tone. A general increase in muscle tone or tremors occurs in more than 90% of patients. Early manifestations of changes in muscle tone include dysphagia, dysarthria, or dystonia. Altered mental status occurs in 75% and can range from agitation to coma. Rhabdomyolysis occurs frequently. White blood cell counts are often increased and may be associated with a left shift. Disseminated intravascular coagulation has been reported. Volume depletion or renal injury from rhabdomyolysis can result in elevated serum urea nitrogen and creatinine concentrations. Various diagnostic criteria have been proposed (**Table 5**), but NMS remains a clinical diagnosis based on exposure to neuroleptic agents or other dopamine antagonists in association with characteristic manifestations.

Table 5. Diagnostic Criteria for Neuroleptic Malignant Syndrome

Major criteria	Minor criteria
Fever	Tachycardia
Muscle rigidity	Abnormal blood pressure
Creatine kinase elevation	Tachypnea
	Altered consciousness
	Diaphoresis
	Leukocytes

Treatment

Dantrolene is the most effective agent for reducing muscle rigidity and decreasing temperature. It is given in the same doses as described for MH. In addition, dopamine agonists have been reported to have beneficial effects in NMS. These drugs include bromocriptine (2.5-10 mg 3 times daily), amantadine (100 mg twice daily), and levodopa-carbidopa. Supportive therapies must also be instituted as indicated. Complications can include respiratory failure, cardiovascular collapse, renal failure, arrhythmias, and thromboembolism. The Neuroleptic Malignant Syndrome Information Service (www.mhaus.org/nmsis) maintains a hotline for medical professionals.

DROWNING, NEAR DROWNING, AND SUBMERSION INJURIES

Drowning is a major public health problem worldwide that results in fatalities and serious morbidities such as neurocognitive impairment.

Definitions

Drowning is defined by the World Health Organization as “the process of experiencing respiratory impairment from submersion or immersion in liquid” regardless of outcome. It is also referred to as *submersion injury*. The older term *near drowning* is still in use; it indicates survival for at least 24 hours following submersion in a liquid medium, regardless of duration and extent of recovery. In this context, *drowning* refers to death within 24 hours, and death after 24 hours is considered to be a *drowning-related death*.

Risk factors for drowning include male gender, young age (children), membership in a minority, physical environment (pool, lifeguards, swimming skill, life jackets, personal flotation devices), alcohol use, and preexisting diseases such as seizures and arrhythmias.

Pathophysiological Process

Pulmonary Effects

Varying degrees of hypoxemia develop as soon as fluid is aspirated. Despite some differences in the mechanisms of lung injury that occur between salt water and fresh water, the net result is similar, with development of noncardiogenic pulmonary edema, varying degrees of surfactant washout (more in fresh water than in sea water), alveolitis and inflammation (more prominent in sea water) with destruction of the capillary membrane, decreased lung compliance, and varying degrees of ventilation-perfusion mismatch. If submersion injury is interrupted within 1.5 to 2 minutes without aspiration by the patient, hypoxemia is immediately reversed after ventilation and circulation are controlled. However, if the injury is prolonged and the aspiration is severe, the lung injury can progress to acute respiratory distress syndrome.

Neurological Effects

The brain is the organ most vulnerable to hypoxic-ischemic injury during the drowning process, and it is the most important determinant of outcome. Patients who arrive to the hospital with coma have higher mortality and greater incidence of persistent vegetative state. A progressive increase in intracranial pressure

(ICP) develops approximately 24 hours after the injury, but control of increased ICP in comatose patients does not improve outcomes.

Cardiovascular Effects

The cardiovascular component of drowning is usually reversible when resuscitation measures are established. As hypoxemia and hypothermia develop, the rhythm ranges from bradycardia and atrial fibrillation to ventricular tachycardia and ventricular fibrillation with cardiovascular collapse.

Renal Effects and Acid-Base Disturbances

Renal dysfunction is a rare complication related to the intensity of the injury. Rhabdomyolysis, myoglobinuria, hemoglobinuria, albuminuria, and acute tubular necrosis have been described depending on the severity of hypoxemia and hypoperfusion accompanying the submersion injury. Metabolic acidosis is common in submersion injury as a result of hypoxemia and hypoperfusion.

Change in Blood Volume and Serum Electrolytes

Significant variations in blood volume and electrolyte balance are uncommon in submersion injury. An estimated 11 mL/kg must be aspirated to cause a notable change in blood volume (increased volume with hypotonic fresh water or decreased volume in hypertonic sea water). It is estimated that approximately 22 mL/kg of water needs to be aspirated to cause pronounced variation in electrolytes. Most patients with submersion injury aspirate close to 3 to 4 mL/kg. Life-threatening electrolyte imbalances can result from Dead Sea submersion injury due to higher water concentrations of sodium, potassium, chloride, calcium, and magnesium.

Hospital Management

Any person with a submersion injury should receive medical evaluation irrespective of his or her immediate condition at the scene. Immediately after submersion, asymptomatic patients may be alert with a normal lung examination and oxygen saturation and may experience no cough or respiratory distress. However, signs of hypoxemia and respiratory insufficiency can develop 4 to 7 hours after the incident. These patients need to be monitored up to 8 hours, and the evaluation should include electrolytes and arterial blood gases. A chest radiograph may be required in selected patients. Symptomatic patients can present with signs and symptoms ranging from anxiety, tachypnea, dyspnea,

persistent cough, and syncope to respiratory distress, hypoxemia, acidosis, seizures, cardiac arrest, and coma.

Resuscitative measures should be continued in the hospital. Intubation should be performed for patients unable to protect their airway. Close examination to identify possible spinal injury as well as other bodily injuries is also important. Hypothermia can be encountered in patients with submersion injury, and rewarming measures should be initiated depending on the severity of hypothermia. Any patient who is deemed symptomatic should be admitted to the hospital for further monitoring of organ function.

Pulmonary Management

If hypoxemia exists without aspiration, it usually resolves after restoration of adequate circulation. Pulmonary edema is common and may benefit from continuous positive airway pressure or noninvasive ventilation. If the patient cannot maintain adequate oxygenation and shows signs of worsening respiratory status, intubation and mechanical ventilation should be initiated. Positive end-expiratory pressure is recommended to decrease ventilation-perfusion mismatch and recruit collapsed alveoli. Mechanical ventilation support also allows alveoli to restore surfactant over time. Steroids have no role in treating drowning-related acute lung injury.

Antibiotic use should be restricted to patients who show signs of infection or who were submerged in grossly contaminated water. Water-based pathogens such as *Pseudomonas*, *Aeromonas*, and *Proteus* are common causes of pneumonia in drowning patients, and initial antibiotic therapy should treat these organisms. *Streptococcus pneumoniae* and *Staphylococcus aureus* have also been reported and usually originate from aspiration of water through the nasopharynx.

Neurological Management

The presence of neurological dysfunction upon presentation, namely altered mental status and absent pupillary reflexes, remains the most important determinant of outcome in drowning. Submersion injury can culminate in cerebral hypoxia, which can progress to cerebral edema and herniation. Goals of management include reversing hypoxemia and hypoperfusion and preventing secondary neurological damage from seizures, hyperglycemia, and increased ICP. Patients should undergo serial neurological examinations. Monitoring of

ICP has been advocated by some clinicians and found unhelpful by others. Any seizure activity should be aggressively treated to avoid worsening cerebral hypoxia. Hyperglycemia (blood glucose >200 mg/dL) on presentation correlates with worse outcome. Management of glucose concentrations should avoid hypoglycemia.

Benefit of induced hypothermia as a neuroprotective intervention after cardiac arrest from drowning has not been established. Further studies are needed to determine the optimal temperature management of patients with hypothermia and coma on presentation. Steroids, barbiturates, and neuromuscular blockers have no role in the management of drowning.

Cardiovascular Management

Hypotension, when present, is usually secondary to hypovolemia, and isotonic fluid resuscitation should be initiated. Vasopressor agents are usually not needed for a long period if circulation is restored. Arrhythmias should be treated appropriately.

Prognosis

No prognostic system has been validated, and it is recommended to continue aggressive resuscitation measures for 48 hours after a submersion injury. A better outcome is noted in patients with the following characteristics: alert on admission, hypothermic, older child or adult, brief submersion time, early resuscitation, early response to resuscitation measures, and submersion in cold water. A worse outcome is noted with the following characteristics: fixed dilated pupils on hospital arrival, submersion time more than 5 minutes, no resuscitation attempts for more than 10 minutes or resuscitation duration greater than 25 minutes, pH less than 7.1, coma on hospital presentation, submersion in water with temperature greater than 10°C (50°F), and higher severity scores. The submersion time and early resuscitation remain the most important determinants of prognosis.

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CHAPTER 42

Sedatives, Analgesics, and Neuromuscular Blockade in the ICU

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Key words: analgesia, analgosedation, benzodiazepines, daily awakening, delirium, dexmedetomidine, opioids, propofol, sedation, sedation scales, spontaneous breathing trials

ANALGESIA IN THE ICU

Patients admitted to the ICU often have multiple causes of pain or discomfort, such as surgery, trauma, bedside procedures, and underlying chronic pain. Development of pain is not exclusive to trauma, surgical, or burn patients, as numerous studies have indicated that patients in the medical ICU frequently experience pain with associated recall. Pain has several physiological and psychological ramifications in critically ill patients. The goal of care for patients experiencing pain should be to limit distress while optimizing patient comfort and minimizing adverse effects. Pharmacological and nonpharmacological therapies can be used for pain management. The analgesic medications commonly used in the ICU have varied pharmacological profiles, each with potential benefits and disadvantages. The ideal analgesic does not exist for all patients, and clinicians must determine the best pharmacological option based on patient-specific factors.

Analgesic Therapy

Both pharmacological and nonpharmacological interventions are important in the management of pain or discomfort in ICU patients. Nonpharmacological therapies are often easy to implement and have few adverse effects. Examples of nonpharmacological interventions include patient positioning, music therapy,

noise elimination, traction for orthopedic injuries and surgeries, and massage. Although nonpharmacological interventions are important, they are often complementary therapies, and most patients require some form of pharmacological therapy to minimize or eliminate pain during their ICU stay.

Pharmacological therapies consist of opioids and nonopioids, each having advantages and disadvantages that must be considered in the selection of the analgesic regimen. In addition to drug-specific characteristics, administration schedule and route of administration are important considerations. Scheduled analgesic therapy is preferred in the ICU because it is more effective to prevent pain than to treat pain that has already occurred. The IV route of administration is preferred given its rapid onset and ease of titration. Oral and transdermal dosage forms can be considered in patients whose acute illness is resolved but who still require analgesia.

Opioid Analgesics

Opioids are the main class of medications used for analgesia in the ICU. These medications provide their analgesic effects mostly through μ-receptor agonism in the central nervous system (CNS). The IV agents predominantly used include fentanyl, hydromorphone, and morphine. **Table 1** lists important clinical and pharmacokinetic parameters for opioid analgesics.

Table 1. Commonly Used IV Opioids

	Morphine	**Hydromorphone**	**Fentanyl**	**Remifentanil**
Equianalgesic dose IV	10 mg	1.5 mg	200 μg	N/A
Time to onset	5-10 min	5-10 min	<1 min	1-3 min
Intermittent dose	1-10 mg every 1-2 h	0.5-2 mg every 1-2 h	25-100 μg every 0.5-1 h	N/A
Continuous infusion dose	1-35 mg/h	0.5-5 mg/h	50-700 μg/h	Loading dose 1.5 μg/kg; maintenance dose 0.5-15 μg/kg/h
Dose adjustment	Renal disease and end-stage liver disease	No	Potential for decreased elimination in hepatic disease Cytochrome P450 enzyme	No

			3A4 substrate: dose requirements affected by inducers and inhibitors	
Active metabolite	Morphine-6-glucuronide	No	No	No
Unique toxicities	Histamine release and hypotension	Potential for dosing errors attributable to higher potency than morphine	Rigidity with high doses, rapid administration	Hyperalgesia

Abbreviation: N/A, not applicable.

Selection of opioid analgesics must be based on factors such as the severity and type of pain, desired onset and duration of analgesia, and patient-specific variables (ie, hemodynamic status and end-organ function). Acute pain is typically best managed with boluses of fentanyl on an as-needed basis due to its quick onset and short duration. Morphine and hydromorphone can be considered for patients who require longer durations of analgesia. Patients who require constant analgesia can be managed with intermittent administration of morphine and hydromorphone. Morphine, hydromorphone, and fentanyl all may be given by continuous infusion, although fentanyl may be the best choice to be administered by this method due to its pharmacokinetic properties. Fentanyl and hydromorphone can be used in hemodynamically unstable patients. Remifentanil is a synthetic opioid with an extremely short duration of action. It undergoes metabolism via plasma esterases, which makes it an ideal agent for patients with organ dysfunction. Because of the short half-life, abrupt discontinuation without tapering may result in breakthrough pain or opioid withdrawal. Rapid development of tolerance and hyperalgesia have been described with use of remifentanil.

Patient-controlled analgesia may be a useful approach to managing pain in postoperative patients with retained cognition and appropriate mental status.

Unlike the other opioid agents, fentanyl is available as a transdermal patch. The patch should not be used for acute analgesia because of a 12- to 24-hour lag time between application and peak effects. Fentanyl patches have been associated with respiratory failure and death in patients who are opioid-naïve and should be

avoided in these patients. In addition, absorption of drug from the transdermal patch is altered with changes in skin temperature, skin permeability, and body habitus. These factors limit the use of the transdermal patch to stable patients with chronic analgesia requirements.

Common adverse effects of opioids include CNS and respiratory depression. These are typically dose-related and of concern in patients who are not intubated. Use of these agents at high doses or by continuous infusion may prolong the time that a patient requires mechanical ventilation. Intermittent dosing, daily interruptions of continuous infusions, and titration by nurses can all prevent unnecessary duration of ventilation.

Morphine should be avoided in patients with renal dysfunction as its active metabolite may accumulate in this population. Morphine should be avoided in elderly patients as well, due to their relative sensitivity to adverse effects at lower doses of the drug. Morphine produces a more pronounced histamine release and results in more hypotension, urticaria, pruritus, flushing, and bronchospasm than the other agents. Therefore, morphine should be avoided in patients with altered hemodynamics.

Constipation is a common adverse effect that occurs in nearly all patients receiving prolonged durations of opioid therapy. A bowel regimen consisting of a stimulant laxative and stool softener should be started in all patients with repeated opioid administration who do not have diarrhea or other contraindications.

Rigidity is an uncommon adverse effect that is most commonly associated with high doses or rapid administration of fentanyl.

True opioid allergy is uncommon. Most reports are associated with morphine, but opioid allergy must be considered with any opioid if a patient develops angioedema or hemodynamic or respiratory compromise following administration. Patients who have symptoms consistent with drug allergy should receive an opioid agent from a structurally unrelated class if further pain relief is needed. Therefore, if a patient has an allergy to hydromorphone, which is a phenanthrene, he or she should not receive therapy with other phenanthrene drugs in the future (ie, morphine).

Many patients present to the ICU with tolerance to opioids and experience acute on chronic pain. Adequately managing these patients' pain is often challenging due to their use prior to hospitalization. These patients should be assessed in

regards to their chronic opioid requirement, which may be administered using their home regimens. Additional opioid analgesics may be administered on an as needed basis to achieve pain control. The optimal regimen varies and should be individualized to each specific patient. Withdrawal is a concern in patients who have received prolonged durations of opioid therapy (>7 days), and these patients should be slowly tapered off of drug (unless it is clinically indicated to continue therapy) and closely evaluated for signs and symptoms of opioid withdrawal.

Two agents that have limited roles in the ICU are meperidine and methadone. Meperidine should be avoided in ICU patients given the risk for accumulation of its active metabolite in patients with renal dysfunction. Meperidine is contraindicated in combination with monoamine oxidase inhibitors or serotonin reuptake inhibitors. The active metabolite for meperidine is neuroexcitatory, and it carries a risk of significant CNS adverse effects. The only role for meperidine in the ICU is in single doses to ameliorate shivering or rigors due to medications, surgery, or hypothermia. Methadone sees minimal use in the ICU. It is typically considered a second-line agent because of its long half-life, drug interactions, and adverse effect profile. It is most commonly used in critically ill patients previously receiving the drug as outpatient therapy. Methadone can also be used in burn and trauma patients to allow for rehabilitation since it has minimal effects on the CNS. Patients may experience significant prolongation of the QT interval when receiving methadone, and its use should be avoided in patients with prolonged QT at baseline or with other medications that have this effect.

Nonopioid Analgesics

Nonopioid analgesics are frequently used as adjunctive therapy in ICU patients. **Table 2** lists commonly used nonopioid analgesics. The most commonly used in the ICU are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). They are typically used as adjunctive therapy in critically ill patients to decrease opioid requirements. Acetaminophen is frequently used outside of the ICU for the treatment of mild to moderate pain. In the ICU, acetaminophen is typically combined with an opioid analgesic and is rarely used alone for analgesia. Adding acetaminophen to an opioid regimen provides better analgesia than increasing the opioid dose alone. Use of IV acetaminophen has been shown to decrease morphine consumption up to 46% in the post-operative period. A small, randomized, controlled study ($n = 40$) comparing meperidine alone to meperidine and IV acetaminophen also demonstrated a faster time to extubation (64.3 ± 40.6 min vs. 204.5 ± 112.7 min) with the combination ($p < 0.01$).

Acetaminophen carries a dose-related risk for hepatotoxicity, and in most patients daily doses should not exceed 4 g/d. In patients with hepatic impairment, history of alcohol ingestion, or poor nutritional intake, total daily doses of acetaminophen generally should not exceed 2 g/d. Data are lacking in regard to long-term scheduled administration and use in non-surgical patients in the ICU.

Table 2. Nonopioids Commonly Used in the ICU

	Ketamine	**Acetaminophen**	**Ibuprofen**	**Ketorolac**	**Gabapentin**	**Carl**
Time to onset	30-40 s	—	—	—	2 h	4-5
Intermittent dose	—	650 mg every 4 h or 1,000 mg every 6 h	400-800 mg every 6 h	15-30 mg every 6 h	100 mg every 8 h (up to 3,600 mg/d)	50- twic to 1 in 4 dos
Continuous infusion dose	0.1-0.5 mg/kg IV followed by 0.05-0.4 mg/kg/h	—	—	—	—	—
Dose adjustment	CYP interactions: substrate 2B6, 2C9, 3A4	2 g/d in patients with underlying hepatic disease	—	—	Requires dose reduction in renal dysfunction	The ran mg Dru inte Sub CY Ind 1A2 2C1 2C9 glyc UG
Unique toxicities	Emergence reactions, hallucinations psychological disturbances, hypertension, tachycardia	Dose-dependent hepatotoxicity	Gastrointestinal bleeding, acute kidney injury	Gastrointestinal bleeding, acute kidney injury	Central nervous system depression	Nys cen ner sys dep Ste Joh syn

							hyp or s ina diu hor ma sup

Abbreviation: CYP, cytochrome P450.

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The analgesic effects of NSAIDs are provided via inhibition of cyclooxygenase. NSAIDs have significant analgesic and antipyretic effects. Adverse effects of NSAIDs include gastrointestinal bleeding, platelet inhibition, and renal insufficiency, which limit their use. Ketorolac is a commonly used IV NSAID in the ICU. Ketorolac is associated with an increased risk of acute kidney injury and gastrointestinal bleeding when used for prolonged durations (>5 days). IV ibuprofen, indomethacin, and diclofenac may be useful for post-operative pain management but data and experience are lacking for routine use for treating pain in critically ill patients.

Neuropathic pain is typically not treated effectively by opioid analgesics. Gabapentin and carbamazepine have shown efficacy in treating neuropathic pain and may be considered in patients with enteral access and no contraindications to therapy.

Ketamine is an *N*-methyl-D-aspartate antagonist and also has activity on μ- and κ-opioid receptors, resulting in a dissociative effect with light sedation and analgesia. In recent years, ketamine has garnered increased interest for ICU analgesia and sedation due to the lack of hypotension and minimal respiratory depression. Although not used frequently, ketamine has been shown to decrease opioid consumption as well as provide better long-term pain control after surgical procedures. The major concerns with using ketamine include hallucinations and other CNS disturbances and cardiac adverse effects, such as hypertension and tachycardia. Despite previous concerns regarding elevations of intracranial pressure (ICP) with ketamine, recent data have demonstrated no associated increase in ICP.

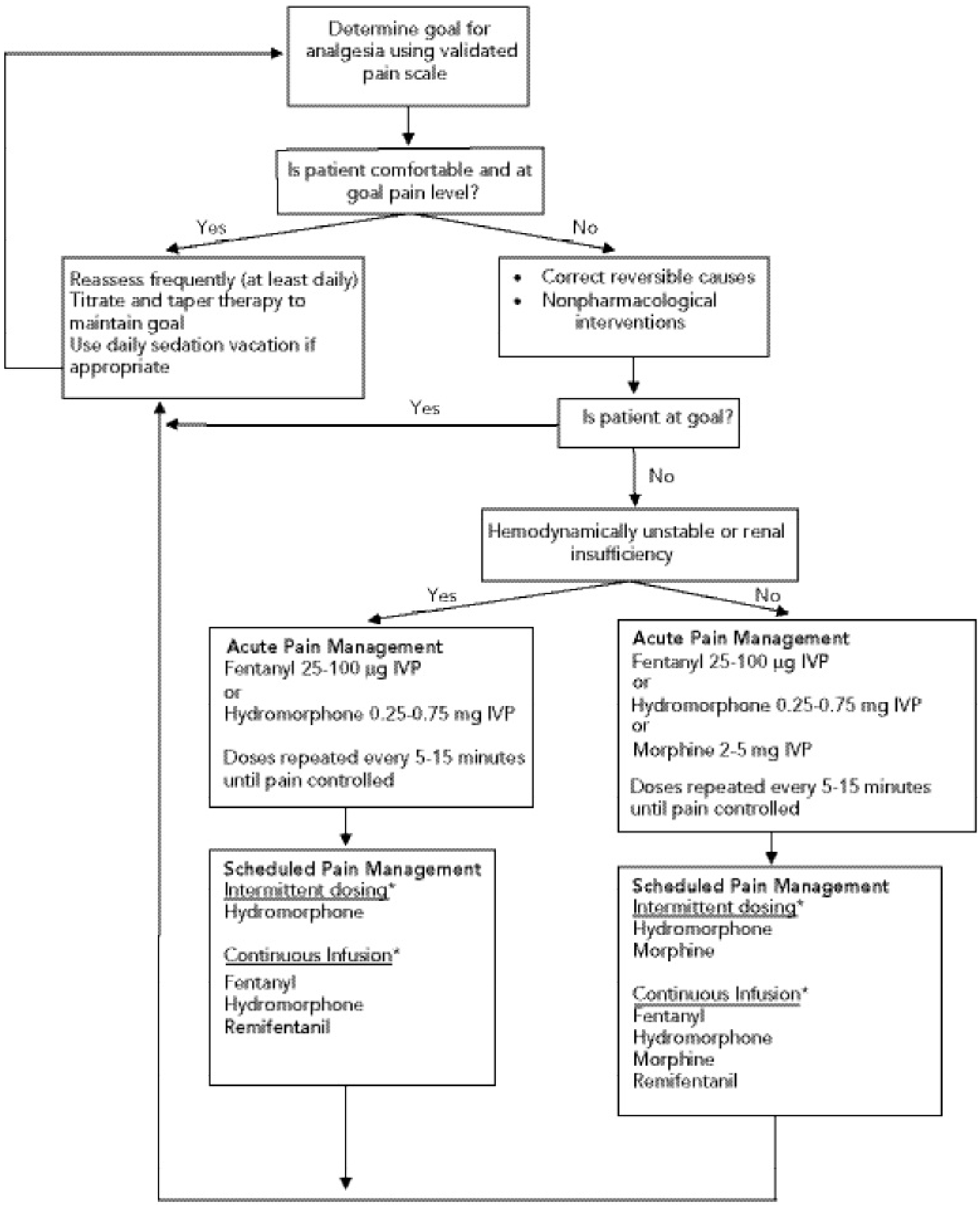
Thoracic epidural anesthesia-analgesia has been shown to be effective in patients

with rib fractures and those undergoing abdominal aortic surgery. The most common adverse effect of this method of analgesia is hypotension, which can be managed by dose reductions and/or fluid boluses.

Assessing Analgesia

Frequent assessment and use of standardized protocols for management are essential in the treatment of pain. An individualized therapeutic plan should be developed with goals that are communicated to all caregivers; the plan should entail frequent documentation of pain assessment and response to therapy and the use of validated assessment scales. **Figure 1** contains an algorithm for the management of analgesia in ICU patients.

Figure 1. ICU pain management algorithm



Opioid doses included in **Table 1.**

Abbreviation: IVP, intravenous push.

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The most reliable method of monitoring pain is patient self-reporting. When assessing pain, one must assess the location, characteristics, influential factors, and intensity. Several tools are used to assess degree of pain intensity. Two commonly used scales are the visual analog scale and the numeric rating scale. The numeric rating scale is commonly used by patients who are able to self-report. It consists of a 0- to 10-point scale, and the patient chooses a number that describes his or her pain. The visual analog scale consists of a horizontal line with descriptive phrases at each end, “no pain” and “severe pain,” which the patient will use to describe his or her pain.

Objective assessments of pain should be performed in patients who are unable to accurately report their pain. The behavioral pain scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) have been validated to assess pain in these situations. The BPS evaluates patients’ facial expressions, upper limb movements, and compliance with the ventilator while the CPOT evaluates facial expressions, body movements, compliance with ventilator or vocalization of pain, and degree of muscle tension. Vital signs should not be used as an assessment alone but may be a cue to further assess pain.

SEDATION IN THE ICU

Indications for ICU Sedation

Agitation and anxiety in the ICU are common and can result from environmental and patient-specific factors. Common environmental factors include continuous audible alarms, poor lighting, interactions with medical and nursing staff, pain, immobility, and interruptions in the normal sleep cycle. Patient-specific factors include delirium, medications, pain, metabolic defects, hypoxia, and drug or alcohol withdrawal. Pharmacological and nonpharmacological interventions are available to manage agitation and anxiety in the ICU. The ideal pharmacological agent varies with patient and clinical scenario, but the goal with any agent should be to minimize agitation and anxiety while also minimizing adverse effects from drug therapy.

Sedative Agents

Frequently used sedatives in the ICU include benzodiazepines, propofol, and dexmedetomidine. Benzodiazepines induce anterograde amnesia by binding to CNS γ-aminobutyric acid (GABA) receptors. The binding of benzodiazepines to these receptors results in the opening of a chloride channel, causing hyperpolarization and stabilization of the neuronal membrane. The most commonly used benzodiazepines in the ICU are midazolam and lorazepam and, less frequently, diazepam. **Table 3** lists the pharmacokinetic parameters, doses, drug interactions, and unique toxicities seen with each agent. Diazepam and midazolam are highly lipophilic, resulting in a very rapid onset of effect (<5 minutes). Diazepam is not recommended for ICU sedation due to the long elimination half-life (20-120 hours) and active metabolite, desmethyldiazepam, which has a half-life of 50 to 100 hours, resulting in a prolonged duration of sedative effect.

Table 3. Sedative Agents Used in the ICU

Variable	Midazolam	Lorazepam	Diazepam	Propofol	Dexmedetomidine
Onset after IV loading dose	2-5 min	15-20 min	2-5 min	1-2 min	5-10 min after 10- to 20-min loading dose
Half-life of parent drug	3-11 h	8-15 h	20-120 h	3-12 h; up to 3 d with prolonged administration	~2 h
Intermittent dose	0.02 – 0.08 mg/kg every 0.5 – 2 h as needed	0.02 – 0.06 mg/kg every 2-6 h as needed	0.03 – 0.1 mg/kg/h every 0.5-6 h as needed	—	—
Continuous dose	Bolus: 0.01 – 0.05 mg/kg mg Infusion: 0.02 – 0.1 mg/kg/h	Bolus: 0.02 – 0.04 mg/kg mg Infusion: 0.01 – 0.1 mg/kg/h	—	Bolus: 5 μg/kg/min over 5 min Infusion: 5-50 μg/kg/min	Bolus: 1 μg/kg over 10 min Infusion: 0.2-1.5 μg/kg/h
Dose adjustment	Renal, hepatic	Hepatic	None	None	Hepatic
Cytochrome	3A4	—	2C19,	2B6	2A6

P450 substrates[a]			3A4		
Unique toxicities	No	Propylene glycol toxicity	No[b]	Hypertriglyceridemia, pancreatitis, hypotension, propofol-related infusion syndrome, egg or soybean allergy	Bradycardia, hypertension with loading dose, lack of respiratory depression

[a]Major interacting enzymes only.

[b]Diazepam does contain propylene glycol, but toxicity is unlikely with intermittent dosing.

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Midazolam has the shortest elimination half-life and, therefore, must be given more frequently if administered intermittently. Midazolam undergoes cytochrome P450 enzyme 3A4 conversion to an active metabolite, α-hydroxymidazolam. The active metabolite is eliminated renally and can accumulate in patients with renal dysfunction leading to prolonged sedative effects. α-hydroxymidazolam is not readily cleared by intermittent hemodialysis but is cleared by continuous venovenous hemofiltration. Additionally, due to its high lipophilicity, midazolam may be stored in adipose tissue and can have prolonged effects in obese patients.

Lorazepam has an intermediate duration of action, allowing for less frequent administration than midazolam. Lorazepam is eliminated by glucuronidation and lacks significant drug interactions. With short-term use, lorazepam has a longer duration of effect than midazolam, but with prolonged exposure (>2 days), lorazepam is associated with shorter time to awakening and less variable effects. The IV formulation contains propylene glycol, which can result in metabolic acidosis and renal failure with commonly used doses (1 mg/kg/d). A serum osmol gap of greater than 10 mOsm/L is an indicator of significant propylene glycol administration.

All of the benzodiazepines cause respiratory depression, potentially hypotension, and may be associated with delirium.

Propofol is a general anesthetic that is also used for sedation in the ICU. Propofol interrupts neural transmission through activity at $GABA_A$, glycine, nicotinic, and muscarinic (M_1) receptors. Propofol has a rapid onset and short

duration of action, making it an easily titratable medication when given as an IV infusion. These properties allow for more rapid neurological evaluation.

Propofol produces respiratory depression and hypotension. Propofol is contained in a lipid emulsion and delivers 1.1 kcal/mL from fat, which must be accounted for when determining nutritional goals in the ICU. Due to the lipophilic nature of propofol, prolonged emergence following discontinuation may occur due to adipose tissue deposition. Given its unique lipid emulsion formulation, propofol is associated with hypertriglyceridemia and pancreatitis. Periodic monitoring of triglycerides and pancreatic enzymes should be considered with use of propofol. Available data are insufficient to determine whether propofol is associated with an increased risk of delirium compared with other sedative agents.

Propofol-related infusion syndrome (PRIS) is characterized by the development of cardiac arrest preceded by a combination of lipemia, lactic acidosis, heart failure, rhabdomyolysis, myoglobinemia, and/or renal failure. While the exact mechanism is not fully understood it is thought to be related to propofol induced mitochondrial dysfunction. Most reports of PRIS occur with high doses (>70 μg/kg/min) for more than 48 hours, although PRIS has been reported with short-term use of lower doses. Due to potential for PRIS at lower doses the current SCCM sedation guidelines recommend a propofol maintenance infusion of 5-50 μg/kg/min which is a reduction from the previous range of 5-80 μg/kg/min. Characteristics that may be associated with an increased risk of death from PRIS include age 18 years or less, male gender, vasopressor administration, cardiac dysfunction, metabolic acidosis, renal failure, hypotension, rhabdomyolysis, and dyslipidemia. Daily monitoring of creatinine phosphokinase has been suggested as a method for early identification of PRIS allowing for propofol discontinuation before full onset of PRIS occurs.

Dexmedetomidine is a centrally acting α_2-agonist that works in the locus coeruleus and spinal cord, inhibiting norepinephrine release and resulting in anxiolysis and analgesia. Dexmedetomidine does not result in deep sedation, amnesia, or respiratory depression but rather allows patients to remain arousable in a “lightly sedated” state. Its use may result in an opioid-sparing effect in surgical patients, but this was not demonstrated in clinical trials of critically ill patients. Dose reductions are recommended in patients with hepatic dysfunction, as medication clearance may be decreased. When compared to benzodiazepines in clinical trials, dexmedetomidine was associated with more bradycardia but there was no difference in the frequency of hypotension. Transient hypertension can occur with the rapid administration of loading doses.

Etomidate is a carboxylated imidazole derivative which exerts it anesthetic effects through GABA receptors. It has a rapid onset of 5 to 15 seconds and short duration of action of 5-10 minutes when given as a 0.2-0.3 mg/kg bolus dose. Etomidate does not cause respiratory depression or acute hypotension when given as single dose. At one time it was administered as a continuous infusion for sedation in the ICU until data published in the early 1980's raised concerns for increased mortality due to adrenal axis suppression. Despite those concerns etomidate continues to be used for rapid sequence intubation due to a favorable pharmacokinetic profile. The use of single dose etomidate for RSI in patients with sepsis is an ongoing topic of debate due to a concern for increased adrenal suppression and possibly mortality. Adrenal axis suppression with etomidate occurs through inhibition of 11- β-hydroxylase and subsequent cortisol formation and can occur with single doses. Available data evaluating etomidate related mortality are limited to just a few small randomized controlled trials and some larger observational studies. A number of recent meta-analyses have evaluated the effects of single dose etomidate with mixed findings. The most recent and largest meta-analysis reported an increased incidence of adrenal suppression with etomidate which was not associated with an increase in mortality. The most common side effect with etomidate for RSI are injection site pain and myoclonus which has been reported in up to 40% of patients.

Sedative Agent Selection

The choice of sedative should be based on a number of factors including the onset, depth, and duration of sedation desired; duration of mechanical ventilation; pharmacokinetic and pharmacodynamic properties; organ function; and cost.

Pain and discomfort are frequently responsible for agitation seen in critically ill, mechanically ventilated patients. Assessment for and elimination of reversible causes for pain should be part of every patient assessment. If pain and agitation persist despite removal of reversible causes, current SCCM sedation guidelines recommend the use of analgesia-first sedation, or analgosedation, for critically ill patients. Available data regarding the impact of analgosedation on ICU outcomes are limited to relatively small studies. The majority of these trials have used remifentanil as the opioid analgesic. Remifentanil is an ideal agent for analgosedation given that it is easily titratable due to a short elimination half-life and clearance is independent of organ function. Remifentanil has been compared to fentanyl plus a rescue sedative regimen in a single trial. There was no difference in mean duration of optimal sedation with similar propofol

requirements between groups. Several studies have compared remifentanil to morphine. The primary endpoints and treatment interventions vary greatly between trials and remifentanil did not demonstrate a consistent benefit across the trials. Given the lack of consistent clinical benefit from small clinical trials with varied primary endpoints, data do not currently support one opioid analgesic over another for analagosedation. Selection of opioid for analgosedation should be based on a patient's clinical scenario and drug-specific characteristics.

A number of small unblinded trials have compared remifentanil with rescue sedation to a more conventional regimen of continuous sedation and analgesia. In these trials analgosedation-based treatment was associated with improved patient comfort, a shorter duration of mechanical ventilation, and decreased ICU length of stay. The need for a traditional sedative varied greatly in these studies but up to 70% of patients receiving analgosedation may require a traditional sedative on an as-needed basis. A single trial has evaluated a regimen of morphine boluses with no sedation compared to propofol infusion plus boluses of morphine with daily interruption of sedation. This trial demonstrated a significant reduction in duration of mechanical ventilation, hospital length of stay, and ICU length of stay with the morphine only regimen. It should be noted that despite these benefits the morphine only group also had a higher incidence of delirium. In addition to the potential benefits listed above, analgosedation allows for a potential reduction in traditional sedative use, thereby decreasing associated adverse effects and allowing for increased mobility.

When a more traditional sedative is required, non-benzodiazepine-based regimens can be considered. They are associated with shortened duration of mechanical ventilation, ICU length of stay (LOS), and hospital LOS and decreased delirium development. Additionally, these regimens allow for more rapid assessment of neurological assessment upon discontinuation.

Propofol has been used routinely as a sedative agent for nearly 3 decades. Despite this, high-quality data evaluating clinical outcomes compared with other sedative agents are lacking. Most early research demonstrated that propofol provides rapid and deep sedation and rapid recovery upon discontinuation. Carson et al demonstrated that propofol paired with a daily sedation vacation reduced the number of ventilator-days but did not affect mortality compared with intermittent lorazepam plus a sedation vacation. Randomized controlled data comparing propofol to dexmedetomidine are limited to a single randomized controlled trial. This trial demonstrated that propofol was noninferior to

dexmedetomidine in achieving and maintaining sedation goals. However, discontinuation due to an inability to adequately sedate patients with maximal study drug and boluses was more frequent with dexmedetomidine. No differences were noted in duration of mechanical ventilation, ICU LOS, or hospital LOS and percentage of patients who were CAM ICU between treatments.

Propofol may be the preferred sedative in several patient groups, including those who require deep levels of sedation, patients with neurological injury for whom rapid neurological reassessment is necessary, and patients with hypertension. Use may be limited in patients with shock due to associated hypotension, bradycardia, and hypertriglyceridemia as discussed previously.

The efficacy and safety of dexmedetomidine for ICU sedation are based on a handful of clinical trials. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial evaluated the effect of dexmedetomidine on the duration of delirium and coma in sedated and mechanically ventilated ICU patients. Patients were randomized to receive dexmedetomidine or lorazepam infusions titrated to achieve their Richmond Agitation-Sedation Scale (RASS) goal (**Table 4**). The study subjects who received dexmedetomidine had more days free of the composite end point of delirium and coma and more days free of coma. Patients also spent more time within 1 point of their RASS goal and were less deeply sedated than patients in the lorazepam arm. No significant difference was found between the 2 groups in regard to duration of mechanical ventilation, ICU LOS, and 28-day mortality. The Safety and Efficacy of Dexmedetomidin Compared with Midazolam (SEDCOM) study group compared the efficacy and safety of long-term dexmedetomidine with midazolam. No difference was noted in duration of time in target sedation range, the primary outcome. The patients receiving dexmedetomidine were extubated faster (3.7 vs 5.6 days, $P = 0.01$) and had less delirium (54% vs 93%, $P < 0.001$), but they required more as-needed midazolam (63 vs 49%, $P = 0.02$). The dexmedetomidine group had more bradycardia but no difference in bradycardia requiring intervention along less hypertension requiring intervention. No significant difference in 30-day mortality was noted between the 2 groups. In another randomized double blinded trial dexmedetomidine was found to be noninferior in achieving and maintaining sedation goals compared with midazolam. Patients receiving dexmedetomidine had a shorter duration of mechanical ventilation compared with those receiving midazolam (123 vs 164 hours, $P = 0.03$), but no differences were found in ICU

LOS, hospital LOS, or percentage of patients with ICU delirium based on the Confusion Assessment Method score of ICU patients (CAM ICU).

Table 4. Richmond Agitation-Sedation Score

Score	Term	Patient Description
+4	Combative	Overtly combative or violent; poses immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters or behaves aggressively toward staff
+2	Agitated	Demonstrates frequent nonpurposeful movements or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert but has sustained (>10 s) awakening, with eye contact, to voice
–2	Lightly sedated	Briefly (<10 s) awakens in response to voice and shows eye contact
–3	Moderate sedation	Moves in response to voice (but no eye contact)
–4	Deep sedation	Does not respond to voice but moves in response to physical stimulation
–5	Unarousable	Shows no response to voice or physical stimulation

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These data demonstrate that dexmedetomidine can be used safely for ICU sedation and results in shorter durations of mechanical ventilation and a lower incidence of delirium. Dexmedetomidine may be the preferred choice in several patient groups, including those who do not require deep levels of sedation, those who develop or are at high risk for delirium, and those in whom suppression of respiratory drive is not needed or desired. The use of dexmedetomidine may not be ideal in patients with deep sedation goals, such as patients requiring paralytics. This is based on data suggesting that dexmedetomidine fails to achieve RASS goals (**Table 4**) less than or equal to –4 more frequently than do

other sedative regimens.

While the 2012 SCCM sedation guidelines recommend nonbenzodiazepine regimens to improve clinical outcomes in mechanically ventilated patients, there may be situations where these regimens are not possible and benzodiazepine-based regimens are preferred. Examples include breakthrough agitation, hypotension, bradycardia, drug or alcohol withdrawal, seizures, chronic benzodiazepine use, or need for deep sedation or amnesia. If benzodiazepines are used, intermittent dosing is preferred over continuous infusions. Midazolam is usually the drug of choice for treatment of acute agitation given its rapid onset and short duration of action. However, obese patients or those with organ dysfunction (renal and hepatic) may have prolonged sedation with the use of continuous midazolam.

Assessing Sedation

The assessment of sedation in critically ill patients is challenging due to various factors. Many patients are unable to communicate effectively, making it difficult for clinicians to recognize anxiety or sources of agitation. Patients who are agitated tend to demonstrate more outward signs of anxiety or discomfort or may have hypertension or tachycardia. They may not cooperate with mechanical ventilation and can develop ventilator dyssynchrony or tachypnea. Given the inherent difficulties with assessing the level of sedation, patients may receive excess medication, resulting in oversedation and a potentially longer duration of mechanical ventilation.

The goal level or depth of sedation varies depending on the clinical scenario. However, the goal for most ICU patients should be ensuring patient comfort while maintaining a light level of sedation. The patient should be arousable to either voice or light stimulation and able to purposefully follow simple commands. Deep sedation, where a patient is minimally responsive to painful stimuli, should be reserved for patients who are paralyzed or have another clinical condition warranting deep sedation, such as acute respiratory distress syndrome with need to suppress ventilator drive. When deep sedation is required, patients should be reassessed at least daily to determine whether they are candidates for a lighter sedation goal.

A number of subjective tools have been developed to optimize sedation assessment. Per the current SCCM sedation guidelines, RASS and Sedation-Agitation Scale (SAS) are the only recommended sedation scales, pending

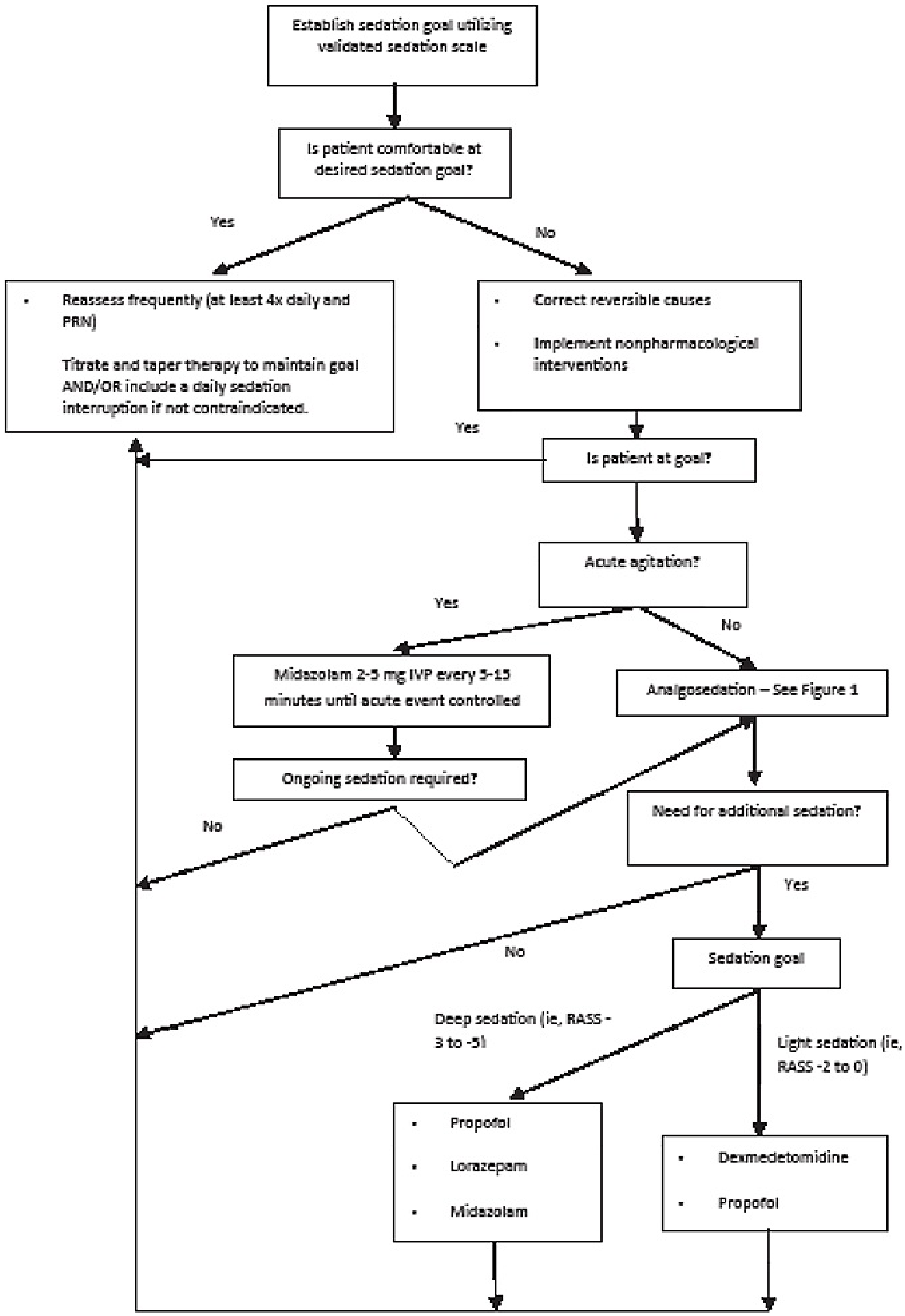
further validation of other scoring systems.

In addition to subjective assessments of sedation, a number of objective measures of brain function exist, such as auditory evoked potentials, bispectral index, Narcotrend Index, Patient State Index, and state entropy. Current data do not support replacement of subjective scoring systems with objective monitors in critically ill patients. Electromyographic artifact may have a significant influence on the objective measures in nonparalyzed patients. This has resulted in poor correlation with subjective assessments and confusion with sedation titration.

Management of Sedation

Appropriate management of anxiety, agitation, and sedation for ICU patients is complex and difficult. **Figure 2** contains an algorithm for the management of sedation in ICU patients. The most important step in this process is completing an accurate assessment using the sedation scores discussed previously. This assessment should be completed at least every 3 hours and on an as-needed basis. An analgesia-based sedation regimen with as-needed sedatives is recommended for most ICU patients. The use of sedative may be considered in patients who do not tolerate or are not candidates for this approach.

Figure 2. Algorithm for the management of sedation in the ICU



Establish sedation goal utilizing validated sedation scale
Is patient comfortable at desired sedation goal?
Yes
No
Reassess frequently (at least 4x daily and PRN)
Titrate and taper therapy to maintain goal AND/OR include a daily sedation interruption if not contraindicated.
Correct reversible causes
Implement nonpharmacological interventions
Yes
Is patient at goal?
Acute agitation?
Yes
No
Midazolam 2-5 mg IVP every 5-15 minutes until acute event controlled
Analgosedation – See Figure 1
Ongoing sedation required?
No
Need for additional sedation?
Yes
No
Sedation goal
Deep sedation (ie, RASS -3 to -5)
Light sedation (ie, RASS -2 to 0)
Propofol
Lorazepam
Midazolam
Dexmedetomidine
Propofol

Sedative doses included in **Table 3.**

Abbreviations: IVP, intravenous push; RASS, Richmond Agitation-Sedation Scale.

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In an effort to minimize oversedation, most patients should have a light sedation goal as determined by a valid and reliable sedation scale. Light sedation goals are associated with improved patient outcomes and allow for interactive patients who are able to participate in mobility programs. Early mobilization programs for mechanically ventilated patients have been associated with improved functional status at hospital discharge and reduced death or hospital readmission 1 year after their critical illness. In addition to light sedation goals, daily sedation interruptions with reassessment of sedative requirements should be considered. The Awakening and Breathing Control (ABC) trial was a multicenter, randomized study combining spontaneous breathing trials with daily awakenings. A total of 335 participants were randomized to either the treatment group which had a daily sedation interruption or spontaneous awakening trial (SAT) plus spontaneous breathing trial (SBT), or the control group which received sedation per usual care and a daily SBT. The treatment group had more ventilator-free days compared with the control group (14.7 vs 11.6, $P = 0.02$) and had shorter durations of ICU and hospital LOS (9.1 vs 12.9, $P = 0.01$; 14.9 vs 19.2, $P = 0.04$). No significant differences were found between the groups in regard to self-extubation, reintubation, or tracheostomy. While the study demonstrated positive benefit of SAT and SBT they had strict eligibility criteria which must be considered prior to implementation. Patients were screened daily for SAT and SBT. Patients were excluded from SAT if they had active seizures, alcohol withdrawal, agitation, neuromuscular blockade, myocardial ischemia or elevated ICP. Patients were excluded from SBT if they were agitated, had an oxygen saturation < 88%, an FiO_2 > 50%, PEEP > 8 cm H_2O, myocardial ischemia, vasopressor use and demonstrated inspiratory efforts. Given the results of these studies and current guideline recommendations, it is reasonable to institute protocols for daily awakenings with spontaneous breathing trials in eligible patients to minimize the duration of sedation, mechanical ventilation, and ICU LOS.

Acute withdrawal reactions upon discontinuation of sedative and analgesic regimens are a potential concern for many ICU patients. While the actual

incidence of sedative and analgesic withdrawal varies between studies, it has been reported to be as high as 32% in one retrospective study of critically ill trauma patients with ICU stays longer than 7 days. In patients with prolonged durations of opioid and sedative administration (>7 days), a strategy should be developed that allows for a gradual discontinuation of agents. The ideal tapering plan must be individualized based on patient and drug characteristics. When sedative and opioid agents are withdrawn from a patient after prolonged durations, the clinician must assess for symptoms of withdrawal, including but not limited to dysphoria, tremor, headache, nausea, sweating, anxiety, agitation, myoclonus, delirium, and seizures. Although the optimal strategy to prevent withdrawal in these individuals is unknown, they should be weaned over several days to minimize the risks of withdrawal.

NEUROMUSCULAR BLOCKADE IN THE ICU

The use of neuromuscular blocking agents (NMBAs) in the ICU remains controversial, with relatively little evidence supporting recommendations for their use. The 2002 SCCM guidelines provide recommendations on the safe and effective use of these medications in critically ill patients.

Indications for Neuromuscular Blockade

The most common indication of neuromuscular blockade is facilitation of mechanical ventilation. Advanced modes of ventilation, severe lung disease, or ventilator dyssynchrony may lead to difficulties that cannot be managed successfully with sedation alone. In addition to being used to facilitate mechanical ventilation, NMBAs have been used to prevent shivering in patients who undergo therapeutic hypothermia after cardiac arrest. These drugs have been used in patients with increased ICP, although the routine use of these medications for this indication has been discouraged. Use of NMBAs has been described in patients with tetanus, drug overdoses, and seizures associated with muscle spasms. No studies have evaluated NMBAs for these indications. However, the 2002 SCCM guidelines recommend the use of NMBAs in critically ill patients to facilitate mechanical ventilation, control ICP, and control muscle spasms when all other options have been tried without success.

In addition to the previously mentioned indications, neuromuscular blockade has been studied in early acute respiratory distress syndrome (≤48 hours duration). A multicentered, randomized, double-blind, placebo-controlled trial of cisatracurium administered as a 15-mg bolus followed by a continuous infusion

of 37.5 mg/h for 48 hours was conducted. Although 90-day mortality was not significantly improved with the drug, the adjusted hazard ratio for death at 90 days was 0.68 (95% confidence interval, 0.48-0.98; $P = 0.04$). Those receiving cisatracurium had more ventilator-free days and more days free from organ failure (not including lungs). In addition, cisatracurium was associated with more days outside the ICU (at 90 days) and less incidence of barotrauma and pneumothorax. The use of NMBA for 48 hours was not associated with an increase in myopathies or other significant adverse effects.

Neuromuscular Blocking Agents

Updated guidelines for the use of neuromuscular blocking agents were published by SCCM at the end of 2016, after the writing of this chapter. Please refer to the new guidelines at: http://www.learnicu.org/SiteCollectionDocuments/Sustained-Neuromuscular-Blockade-Adult-Critically-Ill.pdf.

NMBAs are divided into 2 subclasses: depolarizing and nondepolarizing NMBAs. Depolarizing NMBAs induce paralysis in 2 phases. The first phase (depolarizing phase) occurs when the medication actively depolarizes plasma membranes of muscle fibers, causing contraction. The second phase (desensitizing phase) follows when the muscle endplate develops resistance to depolarization by acetylcholine, and paralysis of the muscle tissue ensues. Succinylcholine is the only available depolarizing NMBA. It is primarily used for rapid-sequence endotracheal intubation or to relax skeletal muscles during surgery. It is not used for continuous neuromuscular blockade in the ICU.

Nondepolarizing NMBAs act as competitive antagonists on motor endplate receptors, blocking the binding of acetylcholine and inactivating the receptors, causing muscle paralysis. Nondepolarizing NMBAs are divided into 2 groups: aminosteroidal and benzylisoquinolinium compounds. **Table 5** lists the pharmacokinetic parameters, doses, and some adverse effects seen with some commonly used nondepolarizing NMBAs.

Table 5. Selected Nondepolarizing Neuromuscular Blocking Agents Used in the ICU

Variable	Atracurium	Cisatracurium	Rocuronium	Vecuronium
Initial dose, mg/kg	0.4-0.5	0.1-0.2	0.6-1	0.08-0.1
Duration, min	25-35	45-60	30	35-45

Elimination route	Hoffman degradation	Hoffman degradation	Renal, hepatic	Renal, hepatic
Dose adjustment	None	None	Decrease infusion rate in hepatic or renal disease	Decrease infusion rate in hepatic or renal disease
Unique toxicities	Seizures due to laudanosine	No	Tachycardia	No

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Nondepolarizing NMBAs can be used as single doses or continuous infusions for extended durations of paralysis. Dosing strategies should be determined based upon the need for prolonged paralysis and the pharmacokinetics of the agent. NMBAs such as vecuronium and rocuronium may be best administered as single intermittent doses, while cisatracurium is more ideal for continuous infusion due to rapid elimination.

Most of the NMBAs are eliminated by the liver and/or kidneys, and use in patients with impairment of these organ systems may result in prolonged neuromuscular blockade. Atracurium and cisatracurium are unique in that they are eliminated through Hoffman degradation. Thus, atracurium and cisatracurium are the drugs of choice in patients with underlying renal or hepatic insufficiency given the limited need for dosage adjustments. Atracurium carries a risk of seizures due to its metabolite laudanosine, which accumulates in renal impairment and prolonged use of the paralytic. Therefore, cisatracurium is typically preferred over atracurium.

A number of adverse effects are associated with the use of NMBAs. Prolonged use of NMBAs has resulted in significant muscle weakness and myopathies. Acute quadriplegic myopathy syndrome is a devastating disorder that can result in months of muscle weakness after discontinuation of NMBAs. Drug holidays and limited durations of use have been advocated to prevent acute quadriplegic myopathy syndrome. Many medications commonly used in the ICU can interact with NMBAs, causing prolonged paralysis. Aminoglycoside antibiotics, corticosteroids, calcium channel blockers, β-blockers, and diuretics can all potentiate the activity of nondepolarizing NMBAs. Therefore, concomitant use of these medications should be minimized. Myositis ossificans can develop from

use of NMBAs and may be prevented with aggressive physical therapy. Anaphylaxis has been reported with a number of NMBAs, with recent data suggesting a higher incidence with use of rocuronium and succinylcholine. Patients receiving these agents should receive prophylactic eye care to prevent keratitis or corneal abrasions as well as agents to reduce the risk of venous thromboembolism.

Monitoring Patients Receiving Neuromuscular Blocking Agents

Monitoring of neuromuscular blockade can be relatively complex. Train-of-four (TOF) monitoring and clinical indicators of blockade should be used to assess the degree of paralysis. The lowest effective dose of NMBAs should be used to provide paralysis. Clinical assessment should include observation of skeletal muscle movement and respiratory efforts. TOF monitoring is accomplished using peripheral nerve stimulation. During TOF monitoring, the device is commonly attached to the ulnar or facial nerve, and then 4 electrical charges are delivered every 0.5 seconds. After the charges are delivered, the contraction of the innervated muscle is graded by palpation or observation. Clinicians should titrate NMBAs to achieve 1 or 2 twitches using TOF monitoring. Limitations of TOF monitoring include altered responses due to edema or perspiration, muscle contraction despite effective blockade, and variability in performance, interpretation, and documentation. Given these potential limitations, the ideal method of monitoring neuromuscular blockade is unclear, and a reasonable approach may be to combine TOF monitoring with clinical assessments such as patient-ventilator interactions.

Because NMBAs do not provide sedation or analgesia, objective measurement of brain function has been utilized. Although many options are available, bispectral index (BIS) monitoring is the most frequently used to assess for adequacy of sedation. Several limitations to the use of BIS in ICU patients exist. Wide ranges of BIS values have been reported, with significant variability between the numbers. It is not always clear whether high BIS numbers correlate with insufficient sedation, discomfort, or residual electromyographic activity. Although not supported by strong evidence, a reasonable goal for titration using BIS is a baseline BIS of 40 to 60 or stimulated BIS of 60 to 70. Current guidelines do not provide a recommendation for or against this method of monitoring brain function as a measure of adequacy of sedation.

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CHAPTER 43

Special Caveats of Drugs Used in Critical Care Medicine

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Key words: pharmacokinetics, pharmacodynamics, guidelines, pharmacoeconomics, therapeutic drug monitoring

This chapter discusses the general administration of drugs for the critically ill patient. Other chapters in this book delineate drug prescribing for specific disease states. This chapter is divided into 2 main sections, the first dealing with the use of published literature in drug decision making and the second with drug monitoring and regimen adjustments. Because many of the topics in this chapter could easily be complete chapters on their own, the topics are covered from an overarching perspective with emphasis on important concepts for the care of critically ill patients.

USE OF PUBLISHED LITERATURE FOR DRUG DECISION MAKING

Use of Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics in Drug Decision Making

Pharmacokinetics is often described as what the body does with a drug, how the drug is absorbed when it is administered by nonintravenous routes, how it is distributed, and how it is metabolized or eliminated. Clinicians unfamiliar with pharmacokinetics often think of this term as synonymous with therapeutic monitoring based on plasma concentrations of drugs. However, relatively few drugs used in an ICU setting are commonly monitored by plasma concentration measurements. The primary value of a rudimentary knowledge of pharmacokinetics is that a clinician is better able to predict changes in drug disposition that are likely to have important clinical consequences necessitating

dosing adjustments or drug discontinuation. This section covers pharmacokinetic issues relevant to the care of patients in the ICU. **Table 1** lists some of the most important pharmacokinetic considerations in the critically ill patient.

Table 1. Pharmacokinetic Considerations in the Critically Ill Patient

Data from pharmacokinetic studies are no substitute for clinical monitoring of the individual patient's response to therapy.
Pharmacokinetic parameters derived from studies involving normal volunteers or less severely ill patients are not directly applicable to the critically ill patient.
Average parameters for volume of distribution and clearance are larger and have much greater variability in critically ill patients compared with less severely ill patients.
The duration of action of single or isolated IV doses of more lipophilic drugs used in the ICU is a function of distribution more than of clearance.
The values for volume of distribution and clearance frequently change from baseline with prolonged drug administration because of factors such as accumulation or altered elimination.
For drugs with active metabolites, the pharmacokinetics of the metabolites as well as the parent compound must be considered.
Drug absorption is important not only with oral or enteral administration but also with intramuscular and subcutaneous injections.

Pharmacokinetic parameters are typically derived from premarketing studies involving small numbers of volunteers or patients with single-system diseases. Critically ill patients with multisystem disease typically have much greater variability in pharmacokinetic parameters such as volume of distribution and clearance. Furthermore, substantial within-patient variability can occur during a relatively short period of drug administration. In general, average values for some parameters (eg, volume of distribution) in critically ill patients tend to be elevated compared with average values in less severely ill patients. For other parameters such as clearance, the variability precludes generalizations, and average doses are lower for some drugs such as argatroban and higher for others such as aminoglycosides, assuming normal renal and hepatic function. These pharmacokinetic differences have important consequences for dosing of a number of commonly used medications, because doses required for therapeutic effect are often at the upper end of suggested ranges for critically ill patients. **Table 2** describes common physiological changes occurring in critically ill patients that alter medication pharmacokinetics, warranting consideration in the

design of dosing regimens.

Table 2. Physiological Effects of Critical Illness on Medication Pharmacokinetics

Physiological Characteristic	Pharmacokinetic Effect	Medication Effect
Hyperdynamic	↑ Clearance	↓ Plasma concentration
Volume overload	↑ Volume of distribution	↓ Plasma concentration
Capillary leak with resultant decreased intravascular volume	↑ Volume of distribution	↑ Plasma concentration
Organ dysfunction	↓ Clearance	↑ Plasma concentration
Catabolism	↑ or ↓ Protein binding	Variable

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A number of pharmacokinetic considerations related to drug administration route, volume of distribution, and clearance are not unique to critically ill patients but are particularly common or problematic in this population. Clinicians are often concerned about oral or enteral drug absorption in critically ill patients but do not appreciate that intramuscular or subcutaneous routes of administration also entail absorption concerns. For example, doses of enoxaparin that achieve target anti–factor Xa concentrations in non–critically ill patients may fail to attain target concentrations in critically ill patients. Tissue edema or receipt of vasopressors impedes absorption of low-molecular-weight heparin in various populations of critically ill patients. These absorption issues present challenges to clinicians, particularly when laboratory monitoring is not available. In the case of the low-molecular-weight heparins, the first signal of inadequate concentrations in the absence of laboratory monitoring is venous thromboembolism, because routine monitoring of factor Xa is not typical.

The termination of effect, as well as onset of action, of single or isolated IV doses of lipophilic medications such as opioids and benzodiazepines is a function of distribution more than of clearance. The implications of this can be demonstrated with the examples of two benzodiazepines, lorazepam and

diazepam. With respect to clearance, both lorazepam and diazepam are metabolized in the liver, but diazepam that is administered for prolonged periods is much more likely to have prolonged effects after drug discontinuation because its half-life is long compared with that of lorazepam (20-40 hours vs 10-20 hours, respectively), and diazepam has an active metabolite with a half-life of 50 to 100 hours. But when these drugs are given as single doses, both the onset and offset of therapeutic effect are more rapid with diazepam than lorazepam because diazepam is more lipophilic and has more rapid distribution to the central nervous system for onset and more rapid redistribution for offset. For a patient with an acute seizure, this means that diazepam will have a more rapid onset of action compared with lorazepam (ie, 1 minute vs 4-7 minutes, respectively), but the offset will also likely occur earlier with diazepam because of redistribution within the central nervous system. An additional consideration for more lipophilic drugs such as fentanyl or propofol is the likely change in values of pharmacokinetic parameters over time due to accumulation from extensive distribution into adipose tissue. This can lead to unpredictable pharmacological effects, or effects that continue for longer than expected, when such drugs are discontinued.

Most medications used in the ICU are cleared by the liver or kidneys, so dosing adjustments are likely to be needed when the function of these organs is impaired or in cases of augmented renal clearance demonstrated by critically ill patients with hyperdynamic physiological status. Whereas recommendations for drug dosing in the setting of augmented drug clearance are scarce, many resources provide recommended dosing adjustments with organ of elimination dysfunction, but virtually all of these resources presume that steady-state drug concentrations have been reached. This includes dosage adjustments based on estimations of creatinine clearance using equations, such as Cockcroft-Gault, that are based on serum creatinine determinations. The applicability of these estimations to critically ill patients is limited by erroneous presumptions of steady-state conditions, as exemplified by daily changes (either increases or decreases) in serum creatinine in addition to alterations in lean muscle mass due to prolonged immobility, paresis, or amputation that affect serum creatinine concentrations. With renal dysfunction, steady-state conditions are unlikely to be reached until the creatinine concentration has stabilized for at least 2 consecutive measurements. Steady-state conditions are needed for reasonably accurate estimates of renal function, given that all currently used equations are based on serum creatinine as a parameter, including the various Modification of Diet in Renal Disease formulas used to estimate glomerular filtration rate. In patients for

whom it is difficult to estimate creatinine clearance, a 24-hour urine collection may provide a more accurate assessment and warrants consideration in patients receiving high-risk medications such as antineoplastics (eg, methotrexate).

Alteration in protein binding is another factor to consider in the dosing of highly protein-bound drugs (eg, >80% binding to albumin) such as phenytoin or valproate. Because protein binding is rarely measured in the clinical setting, formulas have been developed for some highly protein-bound drugs that adjust for low albumin concentrations. One example is phenytoin. It is known that total concentrations of phenytoin are decreased in patients with hypoalbuminemia, but free (unbound) concentrations remain relatively unchanged. Because the free fraction of drugs is usually responsible for therapeutic effect and given that free concentrations are usually unchanged in patients with low albumin concentrations, the usual starting doses (ie, loading and maintenance doses) of phenytoin do not need to be changed if a patient has hypoalbuminemia. However, hypoalbuminemia must be taken into account when one is interpreting blood phenytoin concentrations, because most hospital laboratories measure total (ie, free plus bound) phenytoin concentrations. Relatively simple formulas are available that allow the total phenytoin concentration to be corrected for the low albumin concentration, allowing an interpretation of the phenytoin concentration based on the usual therapeutic range of 10 to 20 mg/L. This calculation aims to account for a reduction in the total (unbound) phenytoin concentration that accompanies a reduction in serum albumin available for phenytoin binding. This calculation can be avoided altogether if the institution's laboratory can analyze free phenytoin concentrations (normal free therapeutic concentrations are 1-2 mg/L assuming 10% albumin binding) in a timely manner. Unfortunately, the situation is more complicated and less predictable for drugs like valproate that not only are highly protein bound but also have saturable binding.

Pharmacodynamic studies are used to investigate the physiological effects of drugs on the body. In the ICU, the primary use of pharmacodynamic information is to dose patients with antimicrobial agents. Dosing information comes from studies that investigate the relationship between agent exposure and microbiological effect using parameters such as the amount of time that the drug's concentration exceeds the minimum inhibitory concentration of the organism (time above MIC) or the ratio of the maximum concentration or area under the concentration-time curve divided by the minimum inhibitory concentration of the organism (AUC/MIC ratio). However, many of these pharmacodynamic targets were derived from animal models, and the optimal

targets for critically ill patients remain unknown, although some data suggest that more aggressive targets may be required in severe infections. Alterations in pharmacokinetic parameters in critically ill patients may reduce the likelihood of attaining these pharmacodynamic targets. For example, a dilutional increase in a patient's volume of distribution may result in a concomitant reduction in tissue levels of hydrophilic drugs, such as β-lactams (eg, piperacillin-tazobactam, cefepime), leading to suboptimal time above MIC at the site of infection. Use of such pharmacodynamic information allows the clinician to optimize dosing regimens through modifications such as administering loading doses, maximizing the size of maintenance doses, or altering the infusion time or frequency. Common examples of dosing by such principles include the administration of aminoglycosides by extended-interval dosing and the administration of β-lactams by intermittent extended or continuous infusions.

Pharmacogenomics, the study of how genes affect patients' response to drug therapies, is an emerging area of practice and research. However, limitations in the availability of real-time testing limit the bedside application of this science in critical care.

Use of Clinical Trials in Drug Decision Making

Data from randomized controlled trials (RCTs) are not available to guide the vast majority of decisions regarding drug choice in critically ill patients, especially for drugs that have been available for many years. When data from RCTs are available for older drugs, there is often a concern of current applicability. For example, the adequately powered RCTs demonstrating the benefits of stress ulcer prophylaxis beyond placebo were published more than 20 years ago. Since that time, many improvements have been made in ICU care, resulting in a reduction in clinically important bleeding in the majority of critically ill patients. Yet stress ulcer prophylaxis continues to be recommended in many guidelines and protocols based on data from these earlier trials.

For newer drugs, approval by the US Food and Drug Administration is often granted based on 2 or more large trials with relatively homogeneous patients, so questions of generalizability often arise. Whether the data from these trials apply to an individual patient can be a challenging question and is often difficult to answer because of issues with study design, such as inadequate power or lack of blinding. For example, early unblinded trials involving remifentanil in critically ill patients suggested benefits in patient outcome beyond older, less costly opioids such as fentanyl; however, more adequately powered and blinded studies

failed to support such benefits. Other study interpretation challenges relate to the sequence of interventions. For example, when an analgesic-based regimen of fentanyl with supplemental midazolam sedation was compared with a sedative-based regimen of midazolam with supplemental fentanyl or morphine analgesia, the analgesic-based regimen was superior. But when remifentanil and fentanyl as primary analgesic-based regimens with supplemental sedation were compared, no differences in patient outcomes were seen. As shown in these examples, interpretation of results is particularly problematic in trials involving supportive care therapies (eg, sedation, analgesia) that do not, or cannot for ethical reasons, involve placebo groups and in which the order and manner of drug implementation are likely to influence the results.

Use of Guidelines and Protocols in Drug Decision Making

Clinicians are increasingly using clinical practice guidelines to make decisions in the ICU. Guidelines are available for supportive care such as analgesia, sedation, and neuromuscular blockade as well as for disease states such as sepsis. However, a number of problems arise related to grading and interpretation of the evidence that forms the basis of these guidelines. No uniform system for grading evidence is available, although attempts have been made to standardize to the GRADE method. Furthermore, the evidence on which recommendations in the guidelines are made is usually of low quantity and quality and frequently is extrapolated from non-ICU settings. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly recommended as opioid-sparing agents for pain treatment, based on studies of patients in a variety of non-ICU settings. Although it is not unreasonable to extrapolate that the same opioid-sparing effects might occur when NSAID-opioid combinations are used in a critically ill patient, the clinician must consider the adverse effect profile of NSAIDs, balancing the risks of gastrointestinal bleeding and renal perfusion reduction against the potential benefits in a given patient.

Systematic reviews and meta-analyses often form the basis for recommendations in guidelines, but these methods also have limitations and are challenging to interpret. Systematic reviews can be very useful for answering specific questions, but it is often difficult to frame drug choices in the ICU in a straightforward way. After its introduction, meta-analysis was initially considered as the highest level of evidence when used in guideline development, but it is currently viewed by most guideline experts as hypothesis generating, even with meta-analyses performed by respected groups such as the Cochrane

Collaboration. Heterogeneity is particularly common in ICU samples under study, and the statistical test for heterogeneity is not powerful (ie, it often suggests homogeneity when in fact it is not present). This became obvious with some of the early meta-analyses involving albumin. Data from subjects of different ages—from premature infants to geriatric patients—were often combined in meta-analyses, and statistical testing suggested that the data were homogeneous even though most clinicians would readily question the validity of combining data from such disparate populations.

Data from national guidelines, systemic reviews, and meta-analyses are often used as the basis for local guidelines or protocols. Institutional guidelines and protocols should be developed and adopted through a systematic process that includes assessing local population characteristics, determining resource availability, and gathering input from key stakeholders rather than simply taking the information from published sources without local discussion.

Use of Pharmacoeconomic and Quality-of-Life Studies in Drug Decision Making

All too often hospitals take a silo approach to cost limitation, with each cost center focusing on reducing its own expenditures, possibly at the expense of other centers. This may cause cost centers to compete for scarce resources, and, most important, it is not a patient-centered approach to care. Of the 4 general types of economic analyses, cost minimization is the most common type used in clinical decision making. Cost minimization typically assumes (often with little supporting evidence) that benefits and risks associated with medications are similar, so the only driver is drug-related costs. An example is the use of continuous-infusion midazolam compared with dexmedetomidine for ICU sedation. Both agents have demonstrated similar efficacy as measured by time spent at target Richmond Agitation-Sedation Scale (RASS) value, but midazolam is far less expensive, which led many institutions to restrict the use of dexmedetomidine as a cost-savings measure. However, given data correlating prolonged benzodiazepine use with increased incidence of delirium and resultant increases in length of stay, days requiring mechanical ventilation, and mortality, these drug cost savings are outweighed by the potential expenses associated with adverse effects.

Given the limitations of cost minimization, other types of economic analyses are preferred but are more difficult to conduct. These include cost-benefit, cost-effectiveness, and cost-utility analyses. Cost-benefit is primarily used for

programmatic justifications because it requires all benefits and risks to be converted to dollar amounts. Cost-effectiveness analysis ideally places all costs, including those associated with adverse effects, in the numerator and places the outcome parameter in the denominator. An example of a question answered by a cost-effectiveness analysis is “For each of 4 sedative interventions, what is the cost to prevent an episode of delirium in a patient admitted with acute peptic ulcer bleeding?” Cost-utility analysis is a variant of cost-effectiveness analysis with a denominator of quality-adjusted life-years. The advantage to cost-utility analysis is that it takes into account patient preferences. Unfortunately, cost-utility analyses are very difficult to perform in the ICU because patients are often unable to communicate their preferences. For clinicians not familiar with interpreting pharmacoeconomic investigations, the most important consideration is whether the assumptions appear to be valid and reasonable for a given population.

DRUG MONITORING AND REGIMEN ADJUSTMENTS

Therapeutic Drug Monitoring and Other Surrogate Markers

A number of caveats and misperceptions surround therapeutic drug monitoring (TDM), beginning with the fact that concentration monitoring is not available for most drugs used in the ICU (**Table 3**). When TDM is available, an all too common occurrence is excessive sampling that does not help to formulate the most appropriate dosing regimen and may even result in inappropriate regimen changes. Most TDM involves measurement of total drug concentration in the blood, although the free drug is usually the active form. This has led some to advocate for monitoring of free concentrations of drugs, a process that is unavailable in many clinical laboratories. Arguments for free concentration monitoring can best be made for drugs with a narrow therapeutic range that are highly protein bound (eg, >80% to albumin), have substantial variation in free drug concentrations within the therapeutic range, and have a small volume of distribution (eg, <2 L/kg). These caveats apply to relatively few drugs (eg, phenytoin, valproic acid). TDM is an adjunct, not a replacement for assessment of clinical response to therapy, and it is often most useful for prevention of adverse events.

Table 3. Considerations With Therapeutic Drug Monitoring (TDM)

Blood concentration measurements are not readily available for the majority of drugs used in critically ill patients.

So-called therapeutic ranges for serum concentrations are typically derived from premarketing studies involving small numbers of non–critically ill patients.
Most therapeutic ranges are based on steady-state drug concentrations obtained at a specific time during the dosing interval, so non–steady-state concentrations can be very difficult to interpret (and are meaningless if drawn at other times).
Disease states that continuously affect a drug's volume of distribution or clearance often negate the presumption of steady-state conditions necessary for proper interpretation of concentrations.
The minimum and maximum concentrations used to define a therapeutic range are often quite arbitrary and not necessarily applicable to a specific patient.
The free or unbound form of a drug is the active form, but the total drug concentration is most commonly measured by clinical laboratories.
Total drug concentrations for a drug with high protein binding (eg, >90%) can be difficult to interpret when protein concentrations are decreased or when other drugs or diseases displace drug.
Clinical response, not a TDM measurement, should be the primary driver of dosing decisions.
The administration and timing of drug doses prior to TDM measurement should be verified, not presumed, because these affect the proper interpretation of the measurement.
TDM is most useful when clinical indicators are misleading or not available or when the clinical indicator is a problem that the clinician is trying to prevent (eg, aminoglycoside nephrotoxicity).
Unnecessary TDM should be avoided (eg, ordering daily measurements of drug concentrations for a drug with a long half-life) because it may lead to inappropriate changes and unnecessary TDM costs.

Surrogate markers of drug response have many of the same limitations as TDM. For some of the most commonly used drugs in the ICU, a remarkable lack of data are available demonstrating a direct and solid relationship between surrogate markers and clinical response. Examples include partial thromboplastin time measurements for unfractionated heparin dosing, anti–factor Xa measurements for low-molecular-weight heparins, and virtually any single hemodynamic or cardiorespiratory parameter used to assess tissue perfusion in patients given fluids or vasoactive agents for shock. In many cases no good alternative to the surrogate marker is available, so the key is appropriate interpretation.

Drug-Drug and Drug-Nutrient Interactions

From a mechanistic standpoint, many potential drug interactions could occur in the critically ill patient, and the challenge for the clinician is sorting out those of clinical importance. **Table 4** lists some of the important drug-drug interactions encountered in the ICU. The table is focused on intravenously administered medications, because this is a common route of administration in critically ill patients and because the number of interactions involving oral medications such as warfarin is too formidable for inclusion in a single table. Furthermore, the table does not include drug-drug interactions that have additive adverse effects on organs such as the gastrointestinal tract (eg, emetogenic) or central nervous system (eg, drowsiness). Of those interactions that are clinically important, another challenge is to decide how to prevent or ameliorate the adverse consequence of the interaction. Fortunately, many interactions that increase or decrease a drug's effects can be managed by careful monitoring of the patient with dosage adjustments as needed based on clinical response. For example, if a patient receiving an opioid for pain is given a sedative agent that causes additive or synergistic central nervous system depression, patient response can dictate decreases in sedative dose, discontinuation of the sedative, or replacement with another agent. Other interactions can be managed through laboratory monitoring. An example is the major interaction that occurs between valproate and carbapenem antibiotics (eg, meropenem). This interaction occurs in a high percentage of patients receiving the two drugs and results in decreases of valproate concentrations, frequently to undetectable levels. Thus, before initiating carbapenem therapy in a patient receiving valproate, the clinician should consider a potential alternative antimicrobial regimen to avoid the interaction, if possible, and should order more intensive monitoring of valproate serum concentrations and possible initiation of an alternate antiepileptic should the combination be clinically unavoidable.

Table 4. Examples of Potentially Serious IV Drug-Drug Interactions in the ICU

Drug Combination	Problem	Mechanism
Amiodarone and β-blockers	Bradycardia, hypotension	Additive β-blockade
Amiodarone and dexmedetomidine	Bradycardia, hypotension	Vagomimetic activity plus β-blockade
Amiodarone and fluconazole	Torsades de pointes	Additive QT prolongation
Amiodarone and phenytoin	Phenytoin toxicity	Inhibition of phenytoin metabolism by

		amiodarone
Amiodarone and quinolones	Torsades de pointes	Additive QT prolongation (rate varies by quinolone)
Dexmedetomidine and β-blockers	Bradycardia, hypotension	Vagomimetic activity plus β-blockade
Digoxin and amiodarone	Digoxin toxicity	Increased digoxin concentrations[a]
Dopamine and phenytoin	Bradycardia, hypotension	Decreased effect of dopamine by phenytoin[a]
Valproate and carbapenems	Decreased valproate levels	Increased valproate clearance

[a]The mechanism is uncertain.

Drug-nutrient interactions are also of concern. A large number of drugs used in the ICU affect gastrointestinal motility. Enteral feedings are often used, raising the potential for tube feeding interactions that impair drug absorption. The majority of these interactions can be prevented by avoiding concomitant feeding and drug administration, but this can be problematic when continuous enteral feeding regimens are used. Less common is the potential for drugs to inhibit the absorption of nutrients from feeding formulations. The usual solution for these interactions is to temporarily discontinue feedings for 1 to 2 hours before and after drug administration via the feeding tube, but clinicians should be cognizant of the effects that frequent feeding interruptions may have on nutritional adequacy.

Drug Clearance in Organ Dysfunction and Extracorporeal Organ Support

The majority of drugs used in the ICU are metabolized by the liver, eliminated by the kidneys, or both. One of the most common interventions by pharmacists is to suggest drug dosing changes for patients with renal dysfunction. The recommended adjustments are usually based on creatinine clearance using estimating equations. Two important considerations for proper interpretation of the values derived from these equations relate to creatinine production and creatinine elimination. The equations presume that creatinine production from creatine is constant and unimpaired, an often misleading presumption in patients who have been immobile for prolonged periods. Furthermore, as with TDM, the

equations almost always presume steady-state conditions (ie, renal function is diminished but stable).

The dosing of renally eliminated drugs is further complicated in patients undergoing intermittent hemodialysis or some form of continuous renal replacement therapy (CRRT). Many drug reference materials provide suggestions for drug dosing in intermittent hemodialysis or CRRT, but as with creatinine clearance estimations, these suggestions typically presume steady-state conditions in the setting of chronic kidney disease as opposed to acute renal failure in which some degree of renal clearance may remain. With some of the high-flux forms of CRRT, such as continuous venovenous hemodiafiltration, drug dosing requirements may be equal to or higher than those needed in patients without renal dysfunction. Much less information is available for adjusting drugs that are eliminated by the liver when hepatic dysfunction is present or in the setting of artificial liver support such as the Molecular Adsorbent Recirculating System (Gambro Lundia AB, Lund, Sweden). Other than trying to avoid unnecessary drugs or known hepatotoxic drugs, the clinician often must base drug-dosing adjustments on clinical response. Fortunately, for most drugs that have hepatic elimination, liver dysfunction must be substantial or the drug must have a relatively narrow therapeutic range before drug substitution becomes necessary. Data regarding drug dosing in patients receiving extracorporeal membrane oxygenation (ECMO) for either cardiac or respiratory indications are extremely limited. The use of fluids (most commonly crystalloids) for system priming and maintenance may result in increased volumes of distribution, which may have implications for hydrophilic drugs. Lipophilic drugs may be more susceptible to interactions with the plastic ECMO circuitry, and circuit sequestration of commonly used analgesic and sedative agents, including propofol, fentanyl, and midazolam, potentially may necessitate dosage increases. However, evidence-based guidance for specific dose adjustments is lacking.

Patient Safety Concerns

Every clinical decision regarding drug administration involves a benefit versus risk assessment. As pointed out earlier in this chapter, the true benefit of a drug for a critically ill patient is often difficult to determine. Also difficult is the assessment of risk, particularly for newly approved drugs. Just as there is a calculation for number needed to treat, there is a calculation for number needed to harm, and ideally this would be part of every benefit-risk assessment.

However, these calculations require known absolute differences between drugs and/or placebo arms of clinical trials, and premarketing studies are unlikely to pick up adverse reactions or adverse drug events (ADEs) that are rare (ie, occurring in <1 in 1,000 patients) but potentially serious. Not until a drug has been marketed and used in large numbers of critically ill patients do the less common ADEs begin to surface. Many of these ADEs are due to medication errors and are preventable, whereas others are unanticipated, unpredictable, and unpreventable. For the latter ADEs, the clinician can only perform close monitoring and consider the possibility of ADEs when unexpected reactions occur. Preventable ADEs can be avoided through proper drug decision making.

Most preventable ADEs are due to system failures, and hospitals have implemented a number of initiatives to reduce these failures. These initiatives include automated infusion devices (so-called smart pumps), computerized prescriber order entry (with order sets and protocols), and bar coding. However, technological innovation is not the only way to address system failures. Other evidence-based improvements include forming an interdisciplinary patient care team that includes a critical care pharmacist and using checklists (**Table 5**). Despite these measures, ADEs continue to occur, although they are inconsistently reported. Reporting techniques that do not rely on clinician reporting, such as a direct observation approach to event detection, demonstrate that there are ongoing concerns and a need for continual quality improvement.

Table 5. Example of Items on an ICU Daily Drug Checklist[a]

Analgesia is effective according to objective assessment.
Sedation level is appropriate.
Patient has been assessed for delirium.
Neuromuscular blocking agents have been evaluated for ongoing indication and appropriate monitoring parameters.
Stress ulcer prophylaxis is indicated or is discontinued.
Venous thromboembolism prophylaxis is ordered or contraindication is documented.
Nutrition and glucose control are adequate.
Bowel regimen is effective.
Vasoactive agents are titrated to specified target parameter.

Indications for and duration of antibiotic use have been assessed.

[a]This is a simple list of items that could be included on an ICU checklist. The presence of an item on the list should not imply that a drug is indicated (eg, neuromuscular blocking agent) but rather that there are issues to address if a person is receiving the drug. More details concerning hospital-specific drug choices and protocols would ideally be included. Other important, nonpharmacological items would be appropriate and necessary for a more general ICU checklist, such as disposition status, mechanical ventilation, and central line care.

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CHAPTER 44

Solid Organ Transplantation in the ICU

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TRANSPLANT-RELATED IMMUNOLOGICAL CHANGES

The immune response consists of innate and adaptive responses. Major contributors to the innate response are the macrophages, neutrophils, natural killer cells, cytokines, and complements. B and T lymphocytes are responsible for the adaptive response, the body's primary defense against foreign antigens. Both immune responses interact and overlap. The adaptive response plays the major role in rejection of solid organ transplant.

Initial T-lymphocyte activation occurs through recognition of the foreign antigen by major histocompatibility complex (MHC) proteins that are part of the cell surface membrane. In humans, MHC proteins are encoded by MHC genes and are known as *human leukocyte antigens* (HLAs), divided into classes I, II, and III. Class I antigens include HLA-A, HLA-B, and HLA-C, whereas class II antigens include HLA-D. Class I antigens express MHC proteins on essentially all nucleated cells; class II antigens are expressed on antigen-presenting cells (APCs), dendritic cells, B lymphocytes, and macrophages; and class III antigens are expressed to help determine the structure of the complement system. An important feature of class I and II MHC proteins is the peptide-binding groove, which is expressed only if a peptide is bound to the groove. Class I MHC proteins bind peptides derived from proteins that are synthesized intracellularly,

whereas class II MHC proteins bind peptides from extracellular proteins that result from endocytosis. The MHC protein and bound peptide (MHC-peptide complex) are necessary to initiate T-cell activation. These peptides can be derived from foreign antigens or self-proteins; however, it is the foreign antigen–derived peptide that initiates T-cell activation in allograft rejection.

The MHC protein is the most potent transplant antigen and has a dominant mode of inheritance. The 2 classes of the MHC gene region are crucial in donor-recipient matching. The allograft may express several class I and class II MHC molecules that are different from those expressed by the recipient. This genetic variability is responsible for graft rejection. Donor-recipient ABO compatibility, HLA typing, and donor-recipient crossmatching are important for graft survival. The recipient's serum is tested for the presence of antibodies against donor red blood cells or HLAs. These anti-HLA antibodies can be found in pregnant patients and patients with exposure to fetal blood, blood transfusions, or previous transplants and are associated with increased risk of hyperacute or accelerated acute rejection.

Allograft rejection is commonly mediated by T cells (CD4-expressing or "helper" T cells and CD8-expressing or cytotoxic T cells). Donor MHC-peptide complex and donor MHC proteins are recognized as foreign antigens and induce an immune response by 2 distinct pathways: direct and indirect allorecognition. Direct allorecognition is the response of recipient T cells to donor MHC-peptide complex on donor APCs within the transplanted graft. This pathway correlates with acute rejection. Indirect allorecognition is the response of recipient APCs that process MHC proteins from donor cells of the transplanted graft and present as peptides to recipient T cells. The indirect pathway is linked to chronic rejection.

Another process called *costimulation* is necessary for T-cell activation. Costimulation involves interaction between ligands and receptors present on cell surfaces of T cells and APCs during the encounter to potentiate the T-cell activation. An example is the ligand-receptor pairing of T-cell CD28 receptors to B7-1 and B7-2 ligands on APCs. These specific interactive pairings are described as one of the most potent signals in regulating T-cell clonal expansion and differentiation as well as inhibition. Further, costimulation of CD40 receptor on APCs and CD40 (CD154, CD40L) ligands on T cells is essential for activation of B cells, dendritic cells, and monocytes. B-cell activation results in antibody production or humoral immunity and cytokine release. In graft rejection, these B-cell processes manifest as hyperacute rejection in the days

immediately following transplant or as acute antibody-mediated rejection at any time after that, but usually within the first 6 months.

Transplant Pharmacological Factors

Transplant protocols aim at providing a high level of immunosuppression early (induction) to prevent rejection or delay the introduction of immunosuppressive agents with undesirable adverse effects. Induction regimens often include an antibody preparation such as basiliximab, rabbit antithymocyte globulin (ATG), or alemtuzumab in combination with corticosteroids.

For long-term immunosuppression, most patients receive a combination of 2 or 3 medications from different classes. The most common combination is the calcineurin inhibitor (CNI) tacrolimus (TAC) and the antimetabolite mycophenolate with or without corticosteroids. Proliferation signal inhibitors are a less commonly used class but provide an alternative when adverse effects prohibit other therapy.

Basiliximab

Basiliximab is a nondepleting, monoclonal immunoglobulin G antibody against the interleukin 2 (IL-2) receptor, CD25, on the surface of activated T cells. The binding of basiliximab inhibits IL-2–mediated activation and proliferation of T cells. Basiliximab is useful as an induction agent but not in the treatment of ongoing allograft rejection.

Antithymocyte Globulin

Rabbit- and equine-derived ATGs are polyclonal preparations against human lymphocytes. The rabbit ATG (rATG) largely predominates. Useful for induction and as a treatment for allograft rejection, rATG acts primarily through depletion of T cells via apoptosis, antibody-mediated cytotoxicity, and complement-dependent lysis.

Dose-limiting leukopenia and thrombocytopenia may result from the use of ATG. Other adverse effects include an infusion-related cytokine release syndrome (CRS), which may be ameliorated by premedication with acetaminophen, antihistamines, and corticosteroids. CRS can produce life-threatening bronchospasm, coronary vasoconstriction, decreased cardiac output, and hypotension. If flulike symptoms occur within the first hours of the first few

doses of ATG, CRS should be considered.

Alemtuzumab

Alemtuzumab, a humanized monoclonal antibody to CD52 found on B cells, T cells, monocytes, and other cell lines, has been used both for induction and for treatment of rejection. Binding to CD52 cells results in lymphocyte depletion. The most common adverse effects include an infusion-related CRS as well as hematological effects such as leukopenia.

Belatacept

Belatacept is a selective T-cell costimulation inhibitor that binds to CD80 and CD86 on APCs, thus blocking the CD28-mediated costimulation of T lymphocytes. Belatacept is used in combination with basiliximab induction and mycophenolate mofetil and maintenance corticosteroid therapy to prevent kidney transplant rejection. Belatacept should be used only in Epstein-Barr virus seropositive patients owing to an increased risk for posttransplant lymphoproliferative disorder in Epstein-Barr virus seronegative recipients. Belatacept carries a boxed warning against use in liver transplant patients due to increased risk of death and graft loss.

As a maintenance immunosuppressant, belatacept is administered monthly via IV infusion following a complex peritransplant regimen. Belatacept is well tolerated and is associated with significantly higher glomerular filtration rate as well as improved patient and graft survival compared with cyclosporine-containing regimens.

Corticosteroids

Glucocorticoids affect the downstream production of various cytokines such as IL-1β, tumor necrosis factor α, IL-2, and IL-6, for example, as a consequence of inhibition of nuclear factor-***k***B. In doses of 250 to 1,000 mg, methylprednisolone is used both in the perioperative period and in the treatment of acute rejection. These large doses are tapered rapidly. Complete steroid withdrawal is achieved in many patients, whereas others are maintained on prednisone 5 mg daily.

Calcineurin Inhibitors

Two CNIs, cyclosporine (CSA) and tacrolimus (TAC), form the backbone of

most immunosuppressive regimens. These agents bind to specific immunophilins, forming a complex with calcineurin and preventing the translocation of nuclear factor of activated T cells and subsequent formation of IL-2, resulting in inhibition of T-cell activation and proliferation.

Both CSA and TAC display a great degree of intrapatient and interpatient pharmacokinetic variability. Poor absorption, for example, is more prevalent in non-Caucasians, whereas children have increased clearance compared with adults. Initial enteral doses for TAC are 0.05 to 0.1 mg/kg twice daily. Cyclosporine micro emulsion doses range from 7 to 9 mg/kg/d in 2 divided doses.

Adverse effects of CNIs include dose-limiting nephrotoxicity and neurotoxicity (including seizures and posterior reversible encephalopathy syndrome). Hypertension and hyperlipidemia are common but occur to a lesser degree with TAC, whereas TAC appears to be more diabetogenic than CSA. Electrolyte abnormalities including hyperkalemia and hypomagnesemia are also seen and tend to be greater with TAC.

The CNIs have a narrow therapeutic window. Therapeutic drug monitoring is a crucial aspect of therapy. These agents are available in a variety of generic and extended-release formulations that are not equivalent. Target concentrations will be dependent on time posttransplant, concomitant therapy, transplanted organ, and the method of analysis (high-performance liquid chromatography vs radioimmunoassay). Goal TAC levels range from 5 to 15 ng/mL, and goal trough CSA concentrations are in the range of 100 to 400 ng/mL, with the highest goal levels being in the first 3 months posttransplant with no antibody induction.

Proliferation Signal Inhibitors

Proliferation signal inhibitors (PSIs) exert their immunosuppressive action by blocking growth factor–induced transduction signals that mediate cell division. Both sirolimus and everolimus bind to intracellular immunophilin FKBP12, forming a complex that binds to a mammalian target of rapamycin, leading to arrest of the cell cycle between the G0 and S phases. This may result in decreased proliferation of hematopoietic and nonhematopoietic cells.

Common adverse effects of the PSIs are leukopenia, thrombocytopenia, and hyperlipidemia (hypertriglyceridemia and increased low-density lipoprotein). Other adverse effects include impaired wound healing, proteinuria, oral ulcers,

and interstitial pneumonitis. Sirolimus is associated with hepatic artery thrombosis early post liver transplant as well as bronchial anastomotic dehiscence in lung transplant recipients. The PSIs also possess antineoplastic, antiviral, and antiatherogenic effects. These properties have led to the use of PSIs in specific situations such as recurrent hepatocellular carcinoma, cytomegalovirus (CMV) infection, and cardiac allograft vasculopathy, respectively.

Both sirolimus and everolimus are hepatically metabolized. Severe liver dysfunction will necessitate dose reduction of both agents by about 50%.

Drug Interactions With CNI and PSI

Drug interactions with immunosuppressive agents primarily involve the CNIs and PSIs and are commonly mediated by cytochrome P-450 3A4 (CYP 3A4) as well as the countertransporter p-glycoprotein. Many commonly used medications inhibit CYP 3A4 and may lead to supratherapeutic concentrations and potential toxicity. The azole antifungals result in increased concentrations of CNIs and PSIs as early as 1 day of concomitant therapy.

The macrolide antibiotics erythromycin and clarithromycin profoundly increase CNI and PSI levels, whereas the interaction with azithromycin appears less severe.

The nondihydropyridine calcium channel blockers verapamil and diltiazem increase levels of CNI and PSI. Amiodarone also has been reported to increase CNI levels. In contrast, the CNIs are inhibitors of CYP 3A4, and increased myopathy with statins has been reported; pravastatin, however, is not metabolized by the same pathway.

Protease inhibitors such as ritonavir are potent inhibitors of CYP 3A4, and their impact on CNI concentrations may be extensive. Patients using ritonavir may require only weekly TAC to maintain therapeutic levels.

Elimination of CNIs and PSIs is enhanced by medications that induce CYP 3A4, such as rifampin, phenytoin, phenobarbital, and carbamazepine. These drugs also can increase the elimination of glucocorticoids. Rejection as a consequence of subtherapeutic levels in the setting of concomitant administration has been described.

Antimetabolites

Azathioprine is converted to 6-mercaptopurine which alters DNA synthesis, thus reducing the production of T cells as well as other cell lines. As such, leukopenia is the major dose-limiting adverse effect. Because xanthine oxidase is responsible for the metabolism of 6-mercaptopurine, concomitant administration of the xanthine oxidase inhibitors allopurinol or febuxostat requires azathioprine dose reduction to avoid toxicity.

Mycophenolic acid derivatives mycophenolate mofetil and mycophenolate sodium have largely replaced azathioprine. Mycophenolic acid inhibits inosine monophosphate dehydrogenase, which blocks purine synthesis and proliferation of T and B cells. Its primary adverse effects are diarrhea, anemia, and leukopenia. Mycophenolate exposure is higher in patients receiving TAC compared with CSA due to CSA-mediated inhibition of enterohepatic recirculation of mycophenolic acid.

RENAL TRANSPLANTATION

Kidney transplantation is the most common solid organ transplant procedure. Admission to the ICU after kidney or simultaneous kidney-pancreas (SPK) transplant is rarely required. The majority of kidney transplant patients admitted to the ICU are there for cardiac monitoring secondary to arrhythmias, myocardial infarction, hypertension control, respiratory distress, or late infectious complications.

Close management of fluids and electrolytes is essential in the immediate postoperative period, and thus monitoring of urine output is crucial. Oliguria must be assessed in a stepwise fashion. The clinician must ensure that the urinary catheter is functioning. If the patient is hypovolemic, volume resuscitation is advised; if the patient is hypervolemic or euvolemic with persisting oliguria, a loop diuretic may be administered.

The development of anuria is an emergency, and imaging to assess the renal blood flow must be obtained. Anuria may be secondary to a urine leak, obstructing lymphocele, arterial or venous thrombosis, or dehiscence of the vascular anastomosis. Urine leaks are usually asymptomatic but may present with a perinephric fluid collection, pain upon voiding, and increasing severity of abdominal or incisional pain. Urine leaks are diagnosed with a voiding cystourethrogram, a nuclear medicine scan, or an elevated creatinine level in a perinephric fluid collection, as compared with serum creatinine. Allograft dysfunction in the early transplant period typically is due to ischemic acute

tubular necrosis, but ACR should be considered.

Hypertension is common in the posttransplant period because of volume expansion in the intraoperative period, medications used for immunosuppression, and treatment of rejection. Urgent hypertension should be treated with an infusion of labetalol or nicardipine. Less urgent hypertension in the postoperative period should be treated with dihydropyridine calcium channel blockers, clonidine, β-blockers, or hydralazine. The use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers can be considered as well and is not contraindicated early in the postoperative course. Blood pressure should not be lowered aggressively, and it is acceptable to allow a slightly higher level of systolic blood pressure early on.

Common electrolyte abnormalities are hyperkalemia, hypophosphatemia, and hypercalcemia. Hyperkalemia is often the result of CNIs or delayed graft function and should be treated medically; if the condition is refractory, dialysis should be initiated. Hypophosphatemia posttransplant is due to autonomous parathyroid hormone production as well as the phosphaturic effect of fibroblast growth factor 23. Levels of less than 1 mg/dL should be treated aggressively with IV phosphorus to avoid respiratory and cardiac depression. Hypercalcemia may occur secondary to tertiary hyperparathyroidism. These patients demonstrate elevated parathyroid hormone levels, hypophosphatemia, and hypercalcemia. Cinacalcet may be considered.

PANCREAS TRANSPLANTATION

Pancreas transplantation remains an alternative therapy for type 1 diabetes mellitus. Pancreas transplant may occur alone (PTA), as part of SPK transplant, or following a kidney transplant (PAK). Ten-year patient and allograft survival rate is greater than 90% for PTA and SPK and is somewhat lower for PAK. The pancreas is surgically implanted intra-abdominally; exocrine drainage is accomplished enterically through an anastomosis of the recipient small intestine and the graft duodenal segment or through the dome of the bladder (duodenocystostomy). Endocrine drainage is accomplished systemically via an iliac or portal vein via the superior mesenteric vein.

Complications

Bleeding most commonly originates from the surgical anastomoses. Graft thrombosis typically presents with graft tenderness, hyperglycemia, massive

hematuria, and decreased urinary amylase levels (in bladder-drained allografts). The treatment is pancreatectomy. Graft leaks present with abdominal pain, fever, and hyperamylasemia. With bladder-drained grafts, the diagnosis is made with computed tomography (CT) of the abdomen with retrograde bladder contrast or low-pressure cystography. In enterically drained recipients, CT of the abdomen with oral contrast is used to establish the diagnosis. The risk of graft pancreatitis is increased in bladder-drained recipients, in grafts with prolonged ischemic time, and with increased donor age and recipient obesity. Elevated amylase, elevated lipase, abdominal pain, graft tenderness, and ileus are seen in these patients. Diagnosis is made via CT of the abdomen with IV contrast. In bladder-drained recipients, late hematuria may represent an infectious duodenal state, such as that caused by CMV. Early hematuria is typically self-limited and due to irritation of the bladder caused by pancreatic enzymes; if hematuria is severe, continuous bladder irrigation may be needed to prevent obstructive clots.

Allograft rejection in the setting of SPK presents with an increase in serum creatinine as well as amylase; hyperglycemia is a late finding. Renal rejection is concurrent, and a kidney biopsy is sufficient to establish the diagnosis. In PAK and PTA, diagnosing rejection is difficult because a pancreas biopsy carries the risk of hemorrhage given the location and intricate vascular structure. In bladder-drained recipients, urine amylase might be measured; otherwise, a biopsy of the head of the pancreas may be needed.

LIVER TRANSPLANTATION

Immediate Posttransplant Critical Concerns

Care of postoperative liver transplant patients can be challenging. These patients are typically in a decompensated state with complex systemic changes. Hyperdynamic vasodilation from liver failure is common. Multifactorial cardiac, pulmonary, and renal dysfunction can be present, complicating perioperative care. Low oncotic pressure and capillary leak hamper the achievement of intravascular euvolemia without concomitant extracellular fluid accumulation. These changes persist after transplant until the allograft begins to function. Significant blood loss, large volume shifts, and electrolyte abnormalities are common perioperatively. Recipients often continue to require liberal fluid and blood product resuscitation to maintain adequate preload and arterial pressure. No consensus is available regarding preferred fluid during this period. However, some authors suggest a combination of non–lactate-containing isotonic

crystalloid combined with an albumin regimen. Vasopressors are often needed with norepinephrine, and low-dose vasopressin is used most often. Intravascular depletion results in poor end-organ perfusion and graft dysfunction. Hypervolemia can be detrimental to the allograft by causing congestion and poor blood flow from the portal to the systemic system. A trend toward negative fluid balance in the initial postoperative period may be associated with improved outcomes. Renal insufficiency is common in these patients. Diuretics or ultrafiltration is helpful in controlling hypervolemia.

Mechanical Problems

Early postoperative transaminasemia is a reflection of the expected ischemic injury sustained during organ procurement. This elevation resolves with graft function. Normalization of prothrombin time and bilirubin indicates graft function as well as normal bile production. Sustained transaminase elevation in the setting of worsening hemodynamics, prolonged prothrombin time, and reduced bile output could signal hepatic artery thrombosis and graft necrosis. Hepatic artery thrombosis needs an emergent diagnosis. Doppler ultrasound is the initial imaging test. If Doppler is not diagnostic, then angiography is necessary to make the diagnosis and hasten revascularization procedures. If thrombosis is present and revascularization fails, emergent retransplant is indicated.

Bile leak is a complication secondary to inadequate surgical anastomosis, ischemia to the distal biliary anastomosis, or stenosis along the biliary tract. Signs include visible reduction or paleness of biliary drainage with an increase in serum aminotransferases and cholestatic enzymes. Ultrasound is the initial test of choice. Options for control include endoscopic and open surgical techniques.

Metabolic Disturbances

Primary graft nonfunction occurs when the allograft is unable to sustain the metabolic responsibilities of the liver. This nonfunction is heralded by worsening coagulopathy and quickly rising serum aminotransferase levels. Hepatic encephalopathy, jaundice, and hypoglycemia are commonly seen. Patients require treatment with fresh frozen plasma, coagulation factors, and IV infusion of dextrose-containing solutions. Emergent retransplant is indicated.

Acute kidney injury and electrolyte disturbances are common after liver transplant. Volume shifts during surgery can result in decreased renal perfusion,

leading to acute tubular necrosis, which may overlap with preexisting renal insufficiency from the hepatorenal syndrome. The clinician must be cautious when introducing and dosing CNIs, which cause vasoconstriction of the afferent arteriole and may contribute to postimplant acute kidney injury. Inhibitors of mammalian target of rapamycin, such as sirolimus and everolimus, can be considered as alternatives in at-risk patients, such as those with preexisting renal impairment. Oliguric or anuric acute kidney injury with volume overload and electrolyte abnormalities requires renal replacement therapy. In hemodynamically compromised or encephalopathic patients, continuous renal replacement therapy is the modality of choice.

Glucose control has been shown to improve graft and overall outcomes in patients undergoing transplant, and outcomes are improved in other ICU patients as well. Parameters for glucose control should be similar to those used for other ICU populations, although transplant patients may have labile glucose levels and need very close monitoring to avoid hypoglycemia.

Immunological Problems

Acute rejection mostly occurs after the seventh postoperative day. Injuries to the bile ducts and vascular endothelium are usually T-cell mediated. Rejection is suspected with a sudden rise in serum aminotransferases and cholestatic enzymes. Liver biopsy is essential to make the diagnosis and shows portal inflammation with neutrophils and eosinophils, endotheliitis, and bile duct injury. Initial therapy consists of high-dose methylprednisolone followed by a taper while ALT, AST, alkaline phosphatase, and total bilirubin levels are monitored. Improvement in these biochemical markers suggests response to treatment. Patients who do not respond to corticosteroids may require repeated induction immunosuppression with antilymphocyte globulin or a similar agent.

Neurological Problems

Hepatic encephalopathy should gradually resolve after successful liver allograft implantation but can recur with primary graft nonfunction, acute rejection, or other causes of graft dysfunction. In the immediate postoperative phase, seizures related to electrolyte abnormalities and intracranial hemorrhage from coagulopathy can occur. Clinicians should avoid overcorrection of chronic hyponatremia because it can lead to the osmotic demyelination syndrome, the manifestations of which are often irreversible and include encephalopathy, dysarthria, paraparesis, and coma. The recommended rate of correction for

hyponatremia that has lasted more than 48 hours is an increase of no more than 9 mEq in plasma sodium over 24 hours and no more than 18 mEq correction in 48 hours. Treatment with IV 5% dextrose in water and desmopressin can help blunt the rate of correction.

Infectious Problems

In the early posttransplant period, infections are the most common causes of morbidity and mortality. Most are healthcare-associated infections, including wound infections, pneumonia, cholangitis, urinary and catheter-related infections, and liver abscesses. *Clostridium difficile* colitis and vancomycin-resistant *Enterococcus* infections are increasingly seen. Reactivation of herpes simplex virus stomatitis is common and requires treatment with antiviral agents such as valacyclovir or acyclovir.

The need for prophylaxis for CMV should be ascertained after review of donor and recipient CMV status. Recipients who are CMV negative and receive a CMV-positive donor liver are at higher risk of infection. Systemic CMV infections occur more commonly at more than 3 weeks after surgery and are characterized by biochemical testing suggestive of graft dysfunction with symptoms of fever and diarrhea. Diagnostic liver biopsy demonstrates characteristic occlusion bodies in the hepatocytes.

As with other types of transplant, the risk for opportunistic infections is highest during the first 12 months after surgery. *Aspergillus* and *Candida* infections and mucormycosis are possible in liver transplant recipients within the first few months of implantation. A bile leak or bowel perforation should be suspected if *Candida* species are found in the peritoneal fluid. Fluconazole is usually used for *Candida* prophylaxis.

LUNG TRANSPLANTATION

The proportion of lung transplant recipients in the United States who are hospitalized in the ICU before transplant has quadrupled in the last decade. In 2013, 4.8% of recipients in the United States were receiving extracorporeal life support (ECLS) at the time of transplant, compared with 0.6% in 2003. With the implementation of the lung allocation score (LAS) in 2005, the proportion of supported patients undergoing transplant has increased, as the need for mechanical ventilation is a heavily weighted factor in the LAS model. Absolute contraindications for bridging with ECLS include irreversible extrapulmonary

organ failure, septic shock, and severe arterial occlusive disease. Patients supported with ECLS may be at risk for development of anti-HLA sensitization and airway dehiscence after lung transplant.

Acute Pulmonary Complications

Early postoperative complications after lung transplant are broad, including primary graft dysfunction (PGD), arrhythmias, infections, extrapulmonary organ failure, anastomotic and pleural complications, and bleeding. Hyperinflation of the native lung is seen in 15% to 30% of patients after single-lung transplant for emphysema. Acute hyperinflation may cause hemodynamic instability and contralateral shift of the mediastinum, leading to compression of the allograft, which can cause atelectasis, hypoxemia, and hypercapnia. Lung-protective, low-tidal-volume mechanical ventilation strategies and early extubation help reduce hyperinflation. Diaphragmatic dysfunction due to phrenic nerve injury is common. The transplanted lung has disrupted lymphatics and is prone to edema. Therefore, negative fluid balance is often the goal.

Primary Graft Dysfunction

A leading cause of early posttransplant mortality is PGD, which affects 10% to 25% of lung transplant recipients and carries a 30-day mortality rate as high as 50%. PGD is characterized by the development of diffuse parenchymal infiltrates and a PaO_2:FIO_2 ratio less than 300 in the absence of cardiogenic pulmonary edema, infection, or hyperacute rejection. PGD is thought to occur because of ischemia-reperfusion injury and is histologically characterized by diffuse alveolar damage. A variety of donor-related risk factors are implicated, including advanced age, a smoking history, prolonged mechanical ventilation, trauma, and hemodynamic instability. Transfusion of blood products, interstitial lung disease, and elevated pretransplant pulmonary artery pressures are recipient-related risk factors. The treatment of PGD is largely supportive; treatment includes lung-protective ventilation strategies and optimization of fluid management with the judicious use of diuretics to reduce extravascular lung volumes. Inhaled nitric oxide and the early use of ECLS may alleviate refractory hypoxemia and are potentially lifesaving. Prevention of PGD remains the key as it is a risk factor for the development of bronchiolitis obliterans syndrome (BOS).

Airway Complications

Anastomotic dehiscence occurs 2 to 4 weeks after transplant, with incidence rates between 1% and 10%. Ischemia is the primary mechanism. Sirolimus and ECLS are also associated with increased incidence. Clinical presentation can include dyspnea, pneumothorax, pneumomediastinum, subcutaneous emphysema, or persistent air leak. Surgical treatment may be needed for severe cases. Incomplete dehiscence may be managed endoscopically.

The incidence of lobar torsion is low. Torsion can be partial with minimal symptoms or can be complete, resulting in total collapse of the lobe. Complete collapse requires immediate surgical intervention to prevent lobar infarction and necrosis.

Lung herniation is a rare complication in which the lung protrudes through an operative scar or a spontaneous intercostal defect formed during periods of increased intrathoracic pressure. Management is usually conservative.

Airway stenosis occurs at the site of the anastomosis in approximately 10% of lung transplant recipients. It usually develops around 3 months after surgery. Alloreactive injury, ischemic damage, and infection are potential causes. CT scan or bronchoscopy can be diagnostic. Symptomatic nonanastomotic narrowing and even complete atresia have been described and are called *vanishing airway syndrome*. This occurs distal to the site of anastomosis, with reported incidence between 2% and 3%. The bronchus intermedius is particularly susceptible because of its relatively narrow lumen.

Infections

Bacterial pneumonia remains the primary cause of mortality in the first month. Gram-negative pathogens such as *Pseudomonas* species, *Klebsiella*, *Escherichia coli*, and *Acinetobacter* and gram-positive pathogens such as *Staphylococcus aureus* are commonly implicated. Late onset of bacterial pneumonia is associated with subsequent development of BOS. Infection with *Mycobacterium tuberculosis* due to reactivation of occult disease in the native lung and infections with nontuberculous *Mycobacterium* are reported; *Mycobacterium abscessus* is the most common nontuberculous pathogen.

CMV is the most common viral pathogen encountered in the posttransplant period. Although all seropositive recipients are at risk, seronegative recipients transplanted with organs from seropositive donors are at the highest risk of developing CMV infection. Treatment consists of a 2- to 3-week course of IV ganciclovir at 5 mg/kg. Prophylaxis in the form of oral valganciclovir is

administered routinely to at-risk patients between 12 weeks and 12 months posttransplant. Epstein-Barr virus is strongly associated with posttransplant lymphoproliferative disease, which has an incidence of 1% to 20%. Clinical presentation of posttransplant lymphoproliferative disease is varied but often similar to that of lymphoma. Treatment consists of decreasing immunosuppression and administering standard chemotherapy. Rituximab can be used for CD20+ cases.

Fungal infections occur in 15% to 35% of lung transplant recipients, with *Aspergillus* and *Candida* species responsible for more than 80% of cases. Early recognition and treatment are important, as the mortality rate for invasive fungal infection can be more than 80%.

Acute Cellular Rejection

Acute cellular rejection (ACR) occurs when recipient lymphocytes react with donor antigens. ACR remains a serious complication as it is the most significant risk factor for the development of BOS. The clinical presentation includes cough, dyspnea, fever, hypoxemia, and rales, with imaging showing ground-glass opacities, septal thickening, and pleural effusions. Bronchoscopic biopsy shows perivascular lymphocytic infiltrates. ACR is a heterogeneous process, so a minimum of 5 biopsy specimens are recommended to provide adequate sensitivity. Treatment of ACR usually consists of pulsed IV steroids followed by a gradual tapering dose over 2 to 3 weeks. Treatment of resistant and persistent rejection remains a challenge, and a variety of strategies are used, including repeat steroids and use of TAC, IL-2 inhibitors, and ATG.

Chronic Pulmonary Complications

Chronic Lung Allograft Dysfunction

BOS is the irreversible, progressive development of obliterative bronchiolitis (OB), leading to a decrease in forced expiratory volume in the first second of expiration (FEV_1) to less than 80%. BOS affects more than half of recipients. Onset is 3 months or more after transplant. Immunological risk factors for BOS include ACR, lymphocytic bronchiolitis humoral rejection and autoimmunity (collagen V sensitization). Nonimmunologic risk factors for BOS include PGD, gastroesophageal reflux, infections, and bronchoalveolar lavage (BAL) neutrophilia. Other phenotypes include restrictive allograft syndrome, neutrophilic allograft syndrome, and fibrous BOS.

Air trapping and mosaic attenuation patterns on high-resolution CT imaging support the presence of BOS but lack sensitivity and specificity. Routine surveillance bronchoscopy is better for early detection. The presence of BAL neutrophilia suggests that OB may be occurring in the lung allograft and that the allograft is at increased risk for progression to BOS. Infection is a confounder and may be the cause of BAL neutrophilia, although infection and OB-BOS may coexist in the allograft. For lung transplant recipients who develop BOS and have evidence of allograft infection, aggressive measures should be taken to treat the infection. For patients who develop BOS while receiving chronic immunosuppression with a regimen that includes CSA, switching to TAC is recommended. A trial of azithromycin administered orally at 250 mg/d for 5 days and then at 250 mg 3 times per week for a minimum of 3 months should be considered. Patients with confirmed gastroesophageal reflux disease should be referred for potential fundoplication. Patients with end-stage BOS that is refractory to other therapies should be evaluated for retransplant.

Recurrence of certain diseases such as sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis can occur. In cases of single-lung transplant, the native lung can be the source of pulmonary complications such as suppurative infections.

Extrapulmonary Complications

Malignancy can occur in the native lung of single-lung transplant patients, and the incidence varies between 7% and 9%. Posttransplant lymphoproliferative disorder encompasses a spectrum ranging from benign polyclonal proliferation of lymphoid tissue to aggressive non-Hodgkin lymphoma, typically of B-cell origin, and occurs in 2% to 8% of lung transplant patients.

CARDIAC TRANSPLANTATION

Patients who undergo cardiac transplant have 1-year and 5-year survival rates of 85% and 80%, respectively. Indications for a heart transplant include end-stage heart failure (New York Heart Association class III or IV) despite optimal medical therapy. Other conditions include acute viral cardiomyopathy, postpartum cardiomyopathy, recurrent life-threatening ventricular arrhythmias despite medical or electrophysiological interventions, primary cardiac tumors, and severe hypertrophic or restrictive cardiomyopathy.

The initial stage of care for the patient entails intraoperative management.

Invasive management should include pulmonary artery catheterization and transesophageal echocardiography, all while avoiding the right internal jugular vein as it will be the portal for subsequent endomyocardial biopsies.

After reperfusion, graft separation from cardiopulmonary bypass usually requires low-dose inotropic support and pacing. Separation is difficult in the presence of graft dysfunction or elevated pulmonary pressures; in this event, high inotropic support, inhaled nitric oxide to reduce pulmonary pressures, intra-aortic balloon pumps, and ventricular assist devices are sometimes required.

The postoperative care in uncomplicated cases is routine, and some patients can be extubated and their drains removed if there is no significant bleeding. Low-dose inotropic support is often required, as initially there is some graft dysfunction, with the right ventricle being more affected. Slightly higher filling pressures (12-15 mm Hg) and pulmonary artery wedge pressures (14-18 mm Hg) are required for a few days. Pressure monitoring is important, as overfilling the heart can induce or worsen tricuspid regurgitation. Slight tachycardia is usually beneficial, as stroke volume is limited with a goal between 90 and 110 beats per minute. Isoproterenol should be used for its pulmonary vasodilation and chronotropic effects. Milrinone or dobutamine with pacing is a good alternative. Atropine and digoxin are ineffective given cardiac autonomic denervation, although β_1 agonists and phosphodiesterase inhibitors remain effective.

In the postoperative period, some degree of vasodilation may be present, and the use of a vasopressor such as norepinephrine may be required. A modest degree of hypotension and vasodilation will help maintain cardiac output in the setting of graft dysfunction but should be avoided in patients with renal dysfunction. Increased pulmonary resistance due to hypoxia or acidosis, accompanied by high intrathoracic pressures, may exacerbate right ventricular dysfunction, and nitroglycerine or milrinone should be considered. Routine use of furosemide can minimize intravascular fluid overload. Patients in oliguric failure may require renal replacement therapy to maintain adequate volume control. Close monitoring of electrolytes is important, as hyponatremia, hypocalcemia, hypomagnesemia, and hypokalemia are common.

In the immediate postoperative period, all precautions should be taken to reduce the risk of infection. Early extubation and removal of intravascular catheters and drains are recommended. Glucose intolerance is common with the use of steroids, CNIs, and β agonists. Glucose should be maintained between 140 and 180 mg/dL. Patients should receive leukocyte-depleted blood to prevent CMV

infection. Immunosuppression regimens usually include triple therapy with CNIs, antiproliferative agents, and steroids. Monitoring of drug levels is important, and surveillance endomyocardial biopsies should be conducted once a week for the first few weeks. Diltiazem has benefits for transplant patients as it retards the development of coronary artery disease and inhibits the metabolism of CNIs. Pravastatin has been shown to improve 1-year survival rates and decrease the incidence of coronary artery disease.

Complications

Graft rejection can be hyperacute, acute, or chronic. The underlying mechanism of the rejection is either cell-mediated rejection or antibody-mediated rejection. The standard of care for adult recipients of heart transplant is to perform periodic endomyocardial biopsy during the first 6 to 12 postoperative months for rejection surveillance. Those who have rejection-induced acute heart failure or hemodynamic instability should be managed with inotropes, pressors, diuretics, and antiarrhythmic medications, according to the clinical presentation. The initial therapy for antibody-mediated rejection includes high-dose IV corticosteroid with plasmapheresis and/or low-dose IV immunoglobulin. Rituximab can be added to reduce the risk of recurrent rejection. Acute symptomatic cellular rejection should be treated with high-dose IV corticosteroid, regardless of International Society for Heart and Lung Transplantation biopsy grade. According to the International Society for Heart and Lung Transplantation guidelines, antithymocyte antibodies should be added in cases of hemodynamic compromise or if clinical improvement does not occur within 12 to 24 hours of IV corticosteroid administration. Treatment for hyperacute rejection should be initiated, preferably when the heart transplant recipient is still in the operating room. Treatments that are considered include high-dose IV corticosteroid, plasmapheresis, immunoglobulin, cytolytic immunosuppressive therapy (CSA, TAC), and metabolic cycle inhibitors (Mycophenolate mofetil).

Nonsurgical bleeding secondary to coagulopathy can result from cardiopulmonary bypass. Cardiopulmonary bypass causes coagulopathy by a decrease in coagulation factors and platelets and by activation of fibrinolysis. Both anticoagulation and hypothermia perioperatively may further exacerbate the abnormal hemostasis. Later in the timeline, left atrial thrombosis occurs in 50% of patients, and systemic embolic events occur in 6% to 14%. Anticoagulation is the main therapy.

Infection causes approximately 20% of the deaths within the first year. Soon after the procedure, prophylactic therapy against *Pneumocystis jiroveci*, herpes simplex virus, and oral candidiasis should begin; CMV-seronegative patients receiving organs from CMV-seropositive donors must be treated with valganciclovir as well. During the first month after transplant, most infections are nosocomial. Various infections, including protozoal, fungal, bacterial, and viral, may occur due to immunosuppression. Patients receiving long-term steroids should be treated with stress-dose steroids during the acute infectious episode.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy is the major cause of death in heart transplant patients after the first year. It is a manifestation of chronic rejection characterized by intimal thickening and fibrosis, leading to luminal narrowing or occlusion of the coronary arteries and graft ischemia. Diagnosis of cardiac allograft vasculopathy is limited by the lack of ischemic symptoms in the denervated allograft and due to underestimation of the extent of the disease during routine coronary angiography. Intravascular ultrasonography is the most sensitive tool and is regarded as the gold standard for the diagnosis of cardiac allograft vasculopathy. Thus, some institutions advocate routine intravascular ultrasonography at 1 month and 12 months after transplant to identify high-risk patients for future cardiovascular events.

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CHAPTER 45

Management of the Severely Injured Trauma Patient

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Key words: neurogenic shock, massive hemothorax, cardiac tamponade, thoracoabdominal stab wounds, damage control laparotomy, abdominal compartment syndrome, ankle brachial index, central cord syndrome

THE INITIAL RESUSCITATION

A trauma resuscitation should always be managed in accordance with Advanced Trauma Life Support (ATLS) guidelines. A primary survey is first conducted through evaluation of the ABCDEs (airway, breathing, circulation, disability, and exposure/environment). The primary survey addresses immediate life-threatening issues and therefore may need to be repeated several times as the clinical scenario progresses. The principle behind the mnemonic is to enforce the priorities of maintaining a patent airway, adequate oxygenation and ventilation, and circulation prior to addressing injuries of lesser severity or distracting injuries.

A is for evaluation of the patient's airway and the need for intubation or control of the airway by surgical means if necessary. Common causes of upper airway obstruction are traumatic injury, occlusion secondary to hemorrhage or foreign body, or a decreased mental status (Glasgow Coma Scale [GCS] score ≤8). Cervical spine precautions must always be maintained while control of the airway is secured.

B is for breathing, which includes evaluation of breath sounds bilaterally, examination of the chest wall and neck veins, and any procedures that may be needed to emergently restore adequate oxygenation and ventilation (such as

needle decompression or chest tube).

C is circulation, which involves evaluating vital signs and pulses in all 4 extremities, addressing active hemorrhage, acquiring adequate IV access (2 large-bore peripheral IVs or central venous access such as a cordis), and evaluating for the source of shock. Circulation may also include any interventions that are needed emergently to control hemorrhage (eg, application of a tourniquet, emergency department thoracotomy).

D is for disability, which is evaluation of neurological status, motor function, and any obvious physical deformities.

E is exposure of the patient, that is, removal of all clothing to evaluate thoroughly for extent of injury. The *E* is also for environmental control, emphasizing the importance of keeping the patient warm by using warmed resuscitation fluids and warming blankets.

Chest and pelvis radiographs as well as a focused assessment sonography in trauma (FAST) or diagnostic peritoneal lavage (DPL) may be part of the primary survey depending on the presenting scenario. The need for a specialist such as a trauma surgeon, neurosurgeon, or orthopedic surgeon or the decision to transfer to a higher level of care if these services are not available should be fairly well delineated by the end of the primary survey. If transfer to a higher level of care is necessary, the goal of patient care should be resuscitation and hemodynamic stabilization rather than diagnostic procedures or testing that would delay transfer.

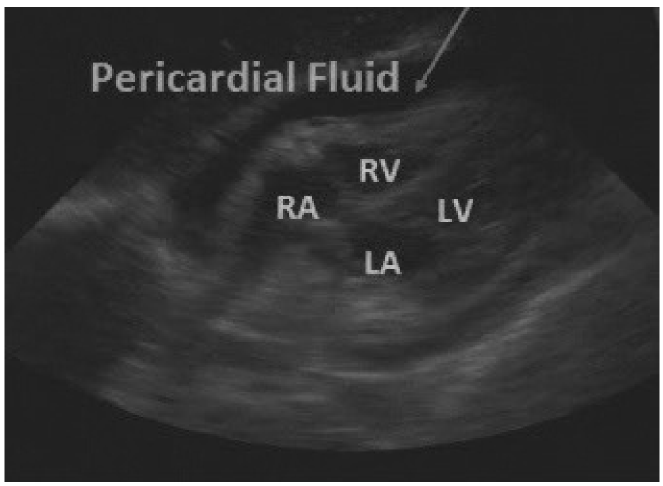
The secondary survey includes a thorough physical examination, an AMPLE history (allergies, medications, past medical history, last meal, and events related to the injury), and imaging. If the patient is unstable and needs to be taken directly to the operating room, the secondary survey may need to be delayed until the life-threatening injuries are addressed. Resuscitation occurs simultaneously throughout the primary and secondary surveys and includes connecting the patient to monitors, drawing laboratory samples, administering fluid or blood products, and placing gastric tubes and urinary catheters.[1,2]

THE FAST EXAM IN THE TRAUMA BAY

The use of ultrasound technology has become the standard of care for the initial evaluation and resuscitation of critically ill trauma patients. The FAST exam has been incorporated into the ATLS secondary survey to rapidly assess for

intraperitoneal hemorrhage and pericardial fluid. Four anatomical views are evaluated: (1) the pericardial view; (2) the right upper quadrant view, to evaluate for perihepatic fluid and Morison pouch (the hepatorenal recess); (3) the left upper quadrant view, to evaluate for perisplenic and perinephric fluid; and (4) the suprapubic view, to assess for pelvic fluid. The FAST has several limitations, in particular inadequate assessment of the retroperitoneum; however, FAST has replaced DPL in the majority of blunt trauma patients. The eFAST (Extended FAST) is practiced in many large trauma centers and includes evaluation of the thoracic cavity for pneumothorax and hemothorax. Ultrasound of the IVC can be used to help assess the volume status of hypotensive patients. Additionally, ultrasound is frequently used for central venous line as well as arterial line placement if the patient is hemodynamically labile (**Figures 1-4**).

Figure 1. Cardiac tamponade



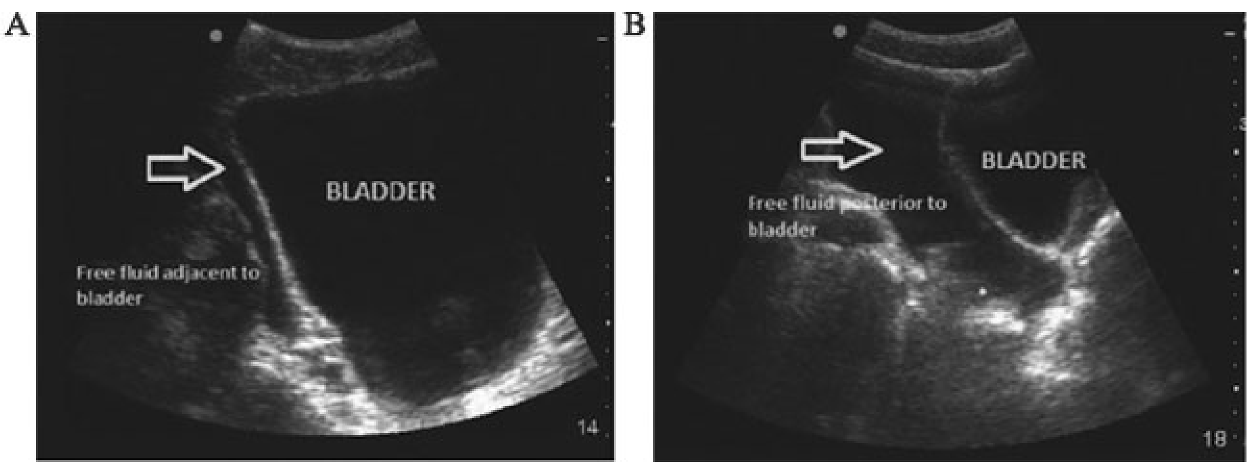
Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

Note pericardial fluid marked with the arrow.

Figure 2. Free fluid in Morison pouch

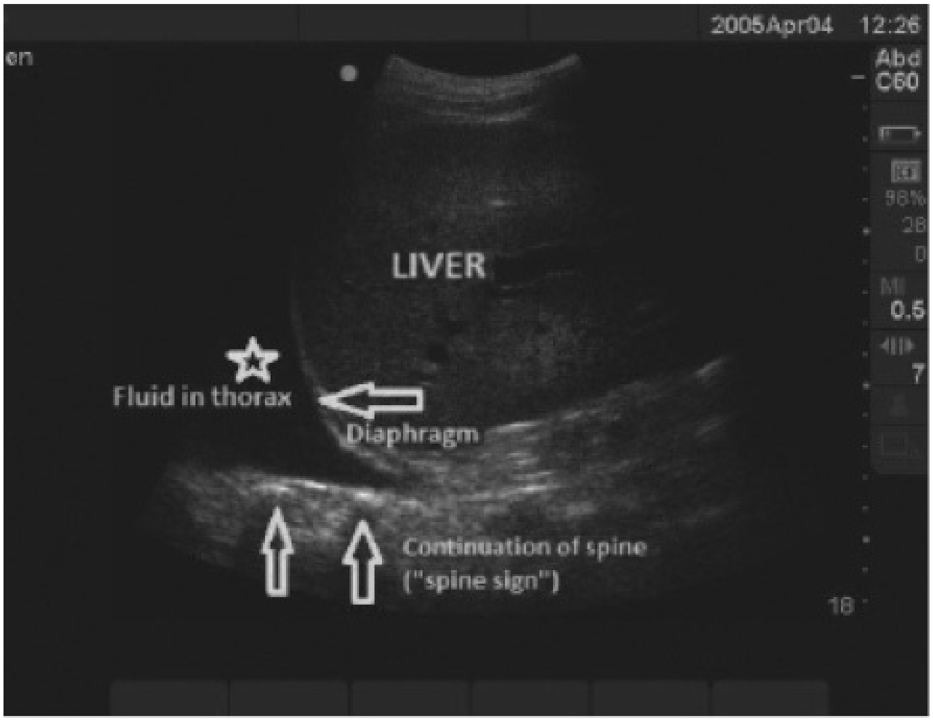
Free fluid is marked in the Morison pouch with a star. Note the fluid's position between the liver and kidney.

Figure 3. Free fluid in pelvis



A) longitudinal view; **B**) transverse view. Free fluid is marked in these images with an arrow.

Figure 4. Pleural effusion in right hemithorase



The fluid is marked with a star. The diaphragm is marked by a left arrow. Note that the spine shadows continue above the diaphragm when there is fluid in the chest. This is known as the “spine sign,” and is an indirect finding when fluid or dense consolidation of lung tissue conducts the sound waves. It will be absent above the diaphragm when there is no fluid in the chest (normal). The liver is labeled.

NEUROTRAUMA

Traumatic Brain Injury

Central nervous system injury is the leading cause of death from traumatic injury, and nearly 2 million traumatic brain injuries occur per year.[3] The GCS should be used to evaluate the patient during the primary survey and then serially for evaluation of decline. Pupillary light response should be documented on admission and monitored for changes. All patients with altered mental status, loss of consciousness, or significant mechanism of injury should receive a computed tomography (CT) scan of the head. Patients who are neurologically intact may defer a head CT only if there is no evidence of posttraumatic amnesia, confusion, or impaired alertness.[4] Refer to **Chapter 3** for details on management of traumatic brain injury.

Evaluation and Management of Vertebral Column Injuries

The primary survey should be completed while the patient is on a backboard with a cervical spine collar in place. Strict spinal precautions must be maintained throughout evaluation, transfer, and rolling of the patient. The majority of spinal injuries occur in more mobile regions of the spine such as the lower cervical spine and the thoracolumbar spine junction. During the primary survey, the spine should be palpated for obvious step-offs, deformities, and tenderness to palpation. The secondary survey should include a complete neurological evaluation for both motor and sensory deficits. CT should be the initial imaging used to evaluate the cervical spine in blunt trauma. If the CT is negative for injury but the patient is clinically symptomatic, magnetic resonance imaging (MRI) of the neck may be used to rule out ligamentous injury.[5] However, cervical spine collars can be removed in obtunded adult trauma patients after a negative high-quality cervical spine CT scan is obtained.[6]

Most severely injured trauma patients with significant mechanism of injury should also obtain CT scans of the chest, abdomen, and pelvis. Digital reconstruction of bony images of these scans can then be used to diagnose injuries in the thoracic and lumbar spine. In alert patients without significant mechanism and no need for further imaging, plain radiographs are adequate to evaluate the thoracolumbar spine. MRI can then be used to further evaluate patients with no obvious findings on CT that are symptomatic or if there is clinical suspicion for ligamentous or spinal cord injury.[7]

Spinal Cord Injuries

Spinal cord injuries are diagnosed clinically by a complete neurological examination, including motor, sensory, and reflex testing. Injuries are classified as either complete, with no motor or sensory function below the level of injury, or incomplete, which entails partial preservation of sensory or motor function caudal to the level of injury with retention of perianal sensation and motor function.

Acute Therapy for Spinal Cord Injury

As with any other trauma, the ABCDEs should be followed. The patient may require intubation to protect the airway. Once the patient is thoroughly evaluated for injury and hemorrhagic shock is ruled out, circulatory support with vasoactive agents may be necessary to avoid secondary ischemic neurological injuries.[8] Methylprednisolone is no longer recommended for use in acute spinal cord injury. Administration of methylprednisolone has not been found to offer

any significant long-term benefit, and several studies have documented more ventilator and ICU days, increased ventilator-associated pneumonias, and increased infections overall.[9]

Incomplete Spinal Cord Injuries

Several incomplete spinal cord injury patterns have been described. Posterior cord syndrome involves injury to the dorsal column with preservation of motor function but loss of proprioception and vibration. Patients have ambulatory difficulties due to lack of proprioception. Anterior cord syndrome entails loss of motor function, sharp pain, and temperature sensation due to injury to the anterior two-thirds of the cord. Patients retain proprioception and sensations of vibration and pressure. Central cord syndrome is usually due to hyperextension in a patient with preexisting spondylosis. The symptoms are global sensory and motor deficits, with the upper extremity function affected more than the lower extremity function. Brown-Séquard syndrome is due to hemitransection of the spinal cord with damage to the corticospinal and spinothalamic tracts. Patients have loss of ipsilateral motor function and contralateral pain and temperature sensation. Conus medullaris and cauda equina syndromes occur with injury to the lumbar region. Patients have variable symptoms of weakness, sensory loss, sexual dysfunction, and bowel and bladder incontinence.[8,10]

Spinal Shock

Spinal shock is a transient impairment of cord function below the level of injury with concomitant loss of sensory and motor function. Patients with spinal shock usually present with initial hypertension followed by hypotension. Symptoms can include flaccid paralysis, incontinence, and often priapism. These usually resolve within 48 hours when the spinal reflexes, such as bulbocavernosus or clitorocavernosus, resume function. Complete injury cannot be determined until resolution of spinal shock.[8,10]

Neurogenic Shock

Neurogenic shock (distributive shock) usually occurs in patients with high thoracic or cervical spinal cord injuries. Autonomic dysregulation leads to hypotension, bradycardia, and usually dry, warm extremities. Loss of sympathetic tone and unopposed parasympathetic output result in vasodilatation and resultant hypotension. Patients also lose the sympathetic input required for reflex tachycardia. The diagnosis of neurogenic shock may be difficult, as

polytrauma patients often have more than one origin of shock, particularly hemorrhagic. Hypovolemic shock alone presents with tachycardia and hypotension. Neurogenic shock presents with low systemic vascular resistance, low stroke volume, and low cardiac output. The central venous pressure may be low or normal. Therapy initially involves replacing intravascular volume. Vasoconstrictors may be used to increase perfusion once other sources of hypovolemia, such as hemorrhage, have been ruled out. Hypotension usually resolves within 24 to 48 hours. Restoration of normotension may curb the progression of cord ischemia and minimize secondary injury to the cord.[8,10]

Autonomic Dysreflexia

This phenomenon occurs in patients with complete spinal cord injury below the level of the sixth thoracic vertebra. Noxious stimuli such as bladder distention or pain result in sympathetic outflow below the level of injury, leading to vasoconstriction and pathological hypertension. Parasympathetic reflex then leads to bradycardia and flushing of the skin. Once this phenomenon is recognized, the stimuli are removed or treated. Intravenous antihypertensive agents can be effective.[8,10]

TRAUMATIC NECK INJURIES

The neck is divided into 3 zones. Zone I extends from the thoracic outlet and clavicles to the cricoid cartilage. Zone II spans the area from the cricoid cartilage to the angle of the mandible. The remaining superior portion of the neck above the angle of the mandible is zone III.

Penetrating Neck Injuries

Penetrating injury to the neck (injuries that penetrate the platysma) have potential for extreme morbidity and mortality in trauma patients given the abundance of vascular, neurological, digestive, and respiratory structures in a compact unprotected space. A missed injury could easily be lethal or lead to severe consequences. As with all trauma, control of the airway should be addressed first. A secure definitive airway is imperative with these injury patterns. The nature of the injury and the hemodynamic stability of the patient will generally dictate the interventions. Life-threatening signs that warrant immediate operative intervention, or “hard signs,” include bleeding, expanding or pulsatile hematomas, subcutaneous emphysema, and stridor. Signs that indicate the need for investigation, or “soft signs,” include dysphagia, widened

mediastinum, hemoptysis, hematemesis, and voice change. If the patient is hemodynamically stable, both zone I and zone III injuries call for a thorough investigation of the aerodigestive tract and vasculature. Computed tomography angiogram (CTA) can be used initially to evaluate the neck vasculature as well as the great vessels. The upper respiratory tract and trachea are assessed via laryngoscopy and bronchoscopy, and the esophagus is evaluated through esophagoscopy and barium swallow. In the past, all zone II injuries that penetrated the platysma were explored in the operating room. Either operative management or selective nonoperative management is now acceptable for asymptomatic and hemodynamically stable patients. The Eastern Association for the Surgery of Trauma (EAST) guidelines give a level 1 recommendation that both selective operative management and mandatory exploration of penetrating zone II injuries are equally safe and justified in seemingly asymptomatic patients.[11,12]

Blunt Injury to the Neck

Three main mechanisms of neck injury are secondary to blunt trauma: direct blunt neck trauma, compression injuries, and, most common, injuries secondary to excessive extension, flexion, or rotation. As with penetrating neck trauma, the airway can easily become compromised, and therefore definitive control is imperative. Physical examination should focus on the hard and soft signs indicative of injury. The clinician should also perform a thorough neurovascular examination, looking for deficits secondary to cerebrovascular injuries. Although aerodigestive injuries are rare, a high index of suspicion must be maintained for these, as missed injuries can have devastating outcomes. Diagnostic techniques are the same for blunt injury as for penetrating injury.

Blunt Cerebrovascular Injuries

Blunt cerebrovascular injuries include injury to the carotid and vertebral arteries. Up until the 1990s, these injuries were believed to be rare, but with increased screening via CTA, many centers now report a greater than 1% incidence in blunt trauma. Signs and symptoms of blunt cerebrovascular injury include neurological deficits, cerebral vascular accident seen on imaging, cervical bruit, expanding hematoma, and oropharyngeal arterial bleeding. Identified risk factors that should prompt screening include displaced facial fractures, basilar skull fractures, seatbelt sign or neck hematoma, hanging injuries, closed head injury with diffuse axonal injury or GCS score less than 6, and high cervical fractures

or ligamentous injuries and fractures that involve the vertebral foramen. The Western Trauma Association has published guidelines, recommendations, and an algorithm for the diagnosis and treatment of blunt cerebrovascular injuries based on observational studies and expert opinion, because no class I data are available regarding management. Screening and diagnosis are conducted by CTA of the neck (at least a 16-slice detector). Equivocal or suspicious findings should prompt an official angiogram. Carotid and vertebral injuries are graded I through V: grade I is luminal irregularity or dissection (<25% narrowing); grade II is dissection or intramural thrombus, intimal flap, or hematoma (≥25% narrowing); grade III is pseudo-aneurysm; grade IV is occlusion; and grade V is transection with free extravasation. Grade V injuries warrant endovascular stent placement, whereas all other grades can be managed with medical therapy only. Recent retrospective data have shown that heparin therapy (partial thromboplastin time 40-50 seconds) and antiplatelet therapy (aspirin and/or clopidogrel bisulfate) are equally effective. CTA is repeated in 7 to 10 days, and if the injury is healed, antithrombotic agents are discontinued. Treatment plans and strategies are not always straightforward in polytrauma patients, especially in those with traumatic brain injuries or those with high risk of hemorrhage secondary to their need for further operative interventions.[13-15]

THORACIC TRAUMA

Life-threatening injuries to the chest should be elucidated within the primary survey by clinical findings, chest radiograph, or FAST examination. Injuries that require immediate action on arrival include tension pneumothorax, massive hemothorax, and cardiac tamponade.

Pneumothorax and Hemothorax

If a patient is in extremis with obvious clinical signs or suspicion of chest trauma, several findings can signal the need for an intervention. Decreased or absent breath sounds or tracheal deviation requires thoracostomy tube placement for relief of tension pneumothorax or hemopneumothorax. A massive hemothorax is defined as chest tube output greater than 1,500 mL upon insertion or greater than 200 mL/h for 4 or more hours and should prompt operative intervention. A chest radiograph is part of the primary survey and can reveal obvious pathological states such as a pneumothorax, massive hemothorax, or pulmonary contusion. An open pneumothorax, or sucking chest wound, should be treated with a sterile occlusive dressing secured on 3 sides to act as a flutter-

type valve to allow air to escape and not reaccumulate secondary to negative pressure. A thoracostomy tube can then be placed at a different location and the wound can be closed.

Cardiac Tamponade

A high level of suspicion for cardiac tamponade should be maintained in patients with a penetrating injury to the "box" (inferior to the clavicles, medial to the nipples, and superior to the lower ribs) or with blunt injury to the chest and hemodynamic instability. Classic signs of cardiac tamponade include hypotension with muffled heart sounds, jugular venous distension, pulsus paradoxus (inspiratory decrease in the systolic blood pressure of >10 mm Hg), and FAST examination findings of pericardial effusion. Pericardiocentesis can be used to temporarily stabilize the patient prior to the operating room; however, the definitive management for traumatic cardiac tamponade is pericardiotomy. The majority of these patients will ultimately require a thoracotomy or median sternotomy.

Patients who are in extremis may require a thoracotomy in the emergency department, an emergency department thoracotomy (EDT) or resuscitative thoracotomy, for loss of vital signs or significant hypotension (<60 mm Hg systolic blood pressure). Since the mortality rate associated with EDT is greater than 95%, the frequency of resuscitative thoracotomies has declined significantly over the past several years. In 2015, EAST published an updated version of evidence-based guidelines for when to pursue EDT. Recommendations are as follows:

1. Strong recommendation for EDT in patients who present pulseless with signs of life after penetrating thoracic injury

2. Conditional recommendation for EDT in patients who present pulseless without signs of life after penetrating thoracic injury, who present with or without signs of life after penetrating extrathoracic injury, or who present with signs of life after blunt injury

3. Conditional recommendation against EDT for blunt trauma without signs of life[16]

These recommendations replace the previous recommendations that EDT should be deemed futile if prehospital cardiopulmonary resuscitation exceeds 10

minutes after blunt trauma without a response, prehospital cardiopulmonary resuscitation exceeds 15 minutes after penetrating trauma without a response, or asystole is the presenting rhythm and there is no pericardial tamponade.[17]

Blunt Aortic Injury

Classic signs on chest radiograph suggestive of a blunt aortic injury include a widened mediastinum, blunting of the aortic knob, an apical cap, depression of the mainstem bronchus, deviation of the nasogastric tube, and cervical rib fractures. CTA of the chest is the diagnostic method of choice for further evaluation of the thoracic cavity and great vessels. Injury is usually at the location of the ligamentum arteriosum, just distal to the takeoff of the left subclavian artery, which is a fixed point of an otherwise mobile aorta. Nonlethal injuries involve intimal and medial tears of the aorta with an intact adventitia. Delayed intervention with open or endovascular repair may be an option in polytrauma patients. Short-acting β-blockers such as esmolol can be used to control blood pressure and heart rate to decrease wall stress and reduce risk of rupture. Treatment options include traditional open repair with interposition grafting via a left posterolateral thoracotomy. In many institutions, thoracic endovascular aortic repair is the preferred procedure. It results in less operative time, less blood loss, and a lower incidence of paraplegia, although long-term data are not available. Endoleak is the most frequent complication after thoracic endovascular aortic repair.[18-20]

Cardiac Injuries

In cardiac injuries, the most common survivable penetrating injuries are stab wounds to the right atrium or right ventricle. Transesophageal echocardiography is helpful with identifying valvular injuries, assessing cardiac function, and defining aortic anatomic features. Blunt cardiac injury should be suspected in all patients with significant thoracic impact and, in particular, those with sternal fractures, cervical or first rib fractures, multiple left-sided or bilateral rib fractures, and hemodynamic instability. An electrocardiogram should be attained, and if the results are normal, no further evaluation is needed. If results are abnormal, a short period of monitoring may be indicated. No strong evidence is available to support the correlation of serial cardiac enzymes with complications. In a symptomatic patient, a transesophageal or transthoracic echocardiograph should be conducted to further evaluate cardiac function and contractility.[20,21]

Esophageal and Tracheobronchial Injuries

Esophageal and tracheobronchial injuries warrant immediate operative intervention. Injuries to the airway can be identified in a patient with a large air leak by chest tube and nonresolution of a collapsed lung or pneumothorax on chest radiograph. Patients may also have extensive subcutaneous emphysema. Injuries can be localized via bronchoscopy and repaired primarily via thoracotomy. A high suspicion for esophageal injury should be considered if the mechanism renders. Barium swallow studies or esophagoscopy should be used to evaluate for tears or perforations, and if injury is identified, a thoracotomy is warranted. If intervention is early, esophageal injuries can be repaired with a double-layer primary closure, usually with pericardium or intercostal musculature mobilized for an overlying flap.[22,23]

Rib Fractures

Rib fractures are the most common thoracic injuries in trauma patients. Flail chest is defined on radiographs as 3 or more rib fractures in 2 or more places, and the pattern has been associated with an increase in mortality. Patients with rib fractures should have aggressive pain control, pulmonary toilet, and volume expansion maneuvers. Those with 4 or more rib fractures who are over the age of 45 are at risk for increased ventilator, ICU, and total hospital days. Implementation of aggressive multidisciplinary protocols has been successful in reducing ventilator days, length of stay, secondary pneumonia, and overall mortality.[24-26]

ABDOMINAL TRAUMA

The abdomen is addressed during the *C* part of the ABCDEs when circulation is assessed to evaluate for possible intra-abdominal injuries. Both physical examination and diagnostic imaging, initially by FAST and then by CT scan if the patient is hemodynamically stable, are used for diagnosis. Physical examination can be unreliable because of multiple factors including head injury, distracting injuries, and intoxication. However, peritonitis, evisceration, and hemodynamic instability with a positive FAST remain indications for exploration after blunt trauma. Penetrating trauma and blunt trauma are managed differently in regard to the workup and the indications for abdominal exploration.

Penetrating Abdominal Wounds

Penetrating wounds primarily consist of gunshot wounds and stab wounds. A FAST should be performed on patients with penetrating injuries; however, the FAST may not be sensitive, and negative examination findings should be validated with further diagnostic techniques.[27] A gunshot wound to the abdomen in an unstable patient mandates operative exploration. If the patient is in extremis or loses vital signs, a resuscitative thoracotomy in the emergency department may be necessary to clamp the thoracic aorta proximally to control intra-abdominal bleeding before transport to the operating room. At the other extreme, if the patient is hemodynamically stable and without signs of peritonitis, a CT scan or laparoscopy may be prudent to evaluate for missile trajectory if there is suspicion that the abdomen has not been penetrated. For penetrating injuries to the back or flank in hemodynamically stable patients with no signs of peritonitis, CT scanning should be done with IV and oral contrast as well as rectal contrast to evaluate the colon. If the abdomen is traversed by the missile, laparotomy is recommended to evaluate for intraperitoneal injury unless fascial penetration is ruled out by CT scan. Stab wounds are managed similarly, although the risk for intraperitoneal injury is less. Operative intervention is necessary for hemodynamic instability, evisceration, or peritonitis. However, if the stab wound is in the anterior abdomen and the patient is stable, a wound exploration should be performed to evaluate for fascial violation. If the fascia has been penetrated, operative exploration, close monitoring with serial examinations, CT scan, and DPL have all been proposed as management strategies. Thoracoabdominal stab wounds, defined as injuries below the level of the nipple, carry the potential for diaphragmatic injury and therefore require some type of diagnostic study. Laparoscopy, thoracoscopy, and DPL have all been described for such cases. When managing stab wounds or items of impalement, clinicians should not remove the knife or object until direct visualization can be accomplished in the operating room.[28,29]

The Decision to Operate: Evaluation of Blunt Abdominal Trauma

Several adjuncts to the physical examination can help to elucidate intraperitoneal injuries in blunt trauma. Details of the mechanism of injury such as intrusion, safety belts, speed, and ejection should be kept in mind during initial examination of the patient. Additionally, findings such as a seatbelt sign, Chance fracture, handlebar injury, and rib fractures should increase suspicion for intra-abdominal injury. The FAST scan is the standard of care in designated trauma

centers, although DPL is still occasionally done and is indicated in unstable patients with 2 negative FAST scans. The standard DPL criteria for operative intervention are more than 100,000 red blood cells, more than 500 white blood cells, or gross blood on the peritoneal aspirate. The FAST scan looks for fluid in the Morison pouch (right upper quadrant), the pelvis, the left upper quadrant, and the pericardium. This scan does not indicate a source, but in a hemodynamically unstable patient, the presence of hemoperitoneum is an indication for emergent laparotomy. When patients who are hemodynamically stable have a positive FAST result, clinicians should order a CT scan to evaluate the source of free fluid. Injuries to solid organs are often managed nonoperatively once the extent of the injury is evaluated by CT. Free fluid without solid organ injury is concerning for bowel injury. Depending on clinical examination, mechanism, and CT findings, these patients should be either explored or monitored closely.[28,30]

Noncompressible Truncal Hemorrhage Control

Until recently, patients presenting with noncompressible truncal hemorrhage had few options for rapid control. Junctional tourniquets, abdominal foam, and resuscitative endovascular balloon occlusion of the aorta (REBOA) are all being studied as adjunctive techniques in patients with exsanguinating hemorrhage. Trauma and acute care surgeons are increasingly using REBOA in civilian settings where balloon occlusion of the aorta can control abdominal or pelvic bleeding (ie, noncompressible truncal hemorrhage arising below the diaphragm) in patients determined to have a bleeding source below the level of the diaphragm. Zones of occlusion in the aorta include zone I (origin of the left subclavian artery to the celiac artery), zone II (celiac artery to the lowest renal artery), and zone III (lowest renal artery to the aortic bifurcation). In hypotensive patients who do not respond to transfusion, a chest radiograph should first be obtained to evaluate for widened mediastinum or a significant pneumothorax or hemothorax. If the chest radiograph reveals concern for hemorrhage arising from the mediastinum, then REBOA should not be performed. If the chest radiograph is negative but the patient has a positive FAST examination, then REBOA should be deployed in zone I. If the FAST examination is negative but a pelvic fracture is present, then zone III REBOA should be deployed. Although the exact role of REBOA is still being evaluated, the centers that are using this technology have reported equivalent if not improved survival compared with resuscitative thoracotomy in patients with noncompressible truncal hemorrhage arising below the diaphragm.[31]

Damage Control Laparotomy

To avoid the “lethal triad” of hypothermia, coagulopathy, and acidosis in trauma patients, damage control surgery has become standard of care. Rather than providing definitive care to injuries, damage control surgery entails initial hemorrhage control, contamination control, and temporary abdominal closure. Once life-threatening injuries are addressed, the patient is transferred to the ICU for resuscitation and restoration of physiological balance. The patient can then be taken back to the operating room for definitive care of injuries in 24 hours or even sooner if hemodynamic parameters stabilize and coagulopathy is corrected. Damage control strategies include controlling bleeding via ligation or repair, suturing or resecting damaged bowel and leaving the patient in discontinuity, removing bleeding solid organs such as kidney and spleen rather than making timely repairs, and packing the liver and possibly the pelvis as necessary to control hemorrhage.

Solid Organ Injuries

Hepatic Injuries

The abdominal organ that most commonly sustains traumatic injury is the liver; however, the majority of hepatic injuries are managed nonoperatively. Liver injuries are graded, with grade I and II injuries being the most common. Mortality rates increase with grade of injury, and grade VI (avulsion) is universally fatal. In 2008, retrospective data from the National Trauma Data Bank revealed that 86.3% of liver injuries are managed without operative intervention.[32] Some groups are now questioning whether the push for nonoperative management in patients with higher grade injury may be associated with an increase in mortality in failures, although this has not been found in all studies. Stable patients should be evaluated first by FAST and then by CT scan. A patient with a CT finding of contrast blush or extravasation may benefit from catheter-directed intravascular therapy with angioembolization, although the precise indications for angiography have not been well defined. Bleeding from liver injuries usually occurs in the first 72 hours. The indication for operation on initial presentation is hemodynamic instability. Operative techniques for major hepatic injuries include initial manual compression while resuscitation is carried out. For patients deemed candidates for damage control, the liver is packed and the patient is taken to the ICU. Postoperative angioembolization should be considered. Cautery, argon beam, and hemostatic agents can be used as adjuncts

for minor bleeding. If hemorrhage is not controlled with compression, the porta hepatis can be clamped (Pringle maneuver) and direct vessel ligation or suture repair performed. If the liver continues to bleed after clamping of the porta hepatis, this indicates that the injury involves the hepatic veins and carries a high rate of mortality. For patients who proceed to immediate operative intervention and damage control, early postoperative CT scanning can identify clinically relevant ongoing bleeding and may be able to guide triage to angiography. Complications of liver injury, whether managed operatively or nonoperatively, include bleeding and abdominal compartment syndrome (ACS) early after injury or infectious complications (hepatic or perihepatic abscess) and biliary complications (biloma, bilehemia, hemobilia, bile ascites, or bile peritonitis) later after injury. These sequelae may require reoperation, percutaneous drainage, or endoscopic retrograde cholangiopancreatography with stent placement or sphincterotomy.[28,33-37]

Splenic Injuries

Splenic injuries are managed primarily nonoperatively; the use of operative intervention depends on hemodynamic stability. In 2008, data from the National Trauma Data Bank revealed that only 10.3% of patients with blunt splenic injury underwent laparotomy upon initial presentation.[32] Bleeding occurs more frequently with higher grade injuries, but all grades of injury can require operative intervention, either at presentation or during a period of observation. Isolated splenic injuries with a blush on CT scan should generally be angioembolized or may require operative intervention if the patient becomes hemodynamically unstable. Those patients with associated intra-abdominal injuries who need operative intervention may require a splenectomy or splenic salvage, depending on the presentation intraoperatively. Splenorrhaphy is another option. Once splenectomy is performed, vaccinations for encapsulated organisms (pneumococcal, *Haemophilus influenzae*, and meningococcal) should be administered.[32,38-40]

Duodenum and Pancreas

Duodenal and pancreatic injuries carry high morbidity if missed on initial presentation. If bile staining or a periduodenal hematoma is seen intraoperatively, a full Kocher maneuver (mobilization of the duodenum) should be performed for exploration. Duodenal hematomas seen on CT can usually be managed with observation and supportive care. If symptoms do not resolve after

approximately 2 weeks, intraoperative drainage of the hematoma should be considered.[28]

The majority of duodenal injuries in the first, third, and fourth portions can be managed by simple repair or resection. If the second portion is involved, the ductal system should be thoroughly evaluated. A pancreaticoduodenectomy, although rare, may be necessary with combined duodenal and pancreatic injuries. Damage control strategies should be used in these patients. Missed pancreatic duct injuries are highly morbid and fraught with long-term complications. Although a CT scan can be suggestive of injury, it is not always diagnostic. Amylase and lipase levels can be followed and may be suggestive of injury if elevated, but they lack specificity. Injuries not involving the pancreatic duct can usually be managed with drainage alone. Injury to the distal pancreas with ductal injury should be managed with distal resection.[28,41]

Stomach

The majority of gastric injuries can be repaired primarily. It is important to enter the lesser sac for full evaluation of the posterior stomach, which can be the location of missed injuries. Other complications can arise after splenectomy if the greater curvature becomes ischemic following ligation of the short gastric vessels.

Small Bowel

Small bowel injuries are amenable to either repair or resection. If the patient is hemodynamically unstable, damage control is often performed and the bowel is left in discontinuity. Definitive repair and anastomosis occur at a later date.

Colon and Rectum

The management of colon injuries has changed dramatically over the past 20 years. Simple lacerations and perforations can be debrided and closed primarily, and in patients with extensive injuries requiring resection, anastomoses can be performed if the patient is hemodynamically stable. In unstable patients, damage control techniques may be necessary with delayed anastomosis or colostomy. The management of rectal injuries has remained relatively constant given the amount of morbidity and mortality associated with pelvic sepsis. High suspicion should always be maintained for rectal injuries, especially in penetrating trauma and pelvic fractures. Evaluation of suspected injuries should include a thorough

rectal examination and rigid proctosigmoidoscopy. Management includes colonic diversion, debridement of nonviable tissue, and closure if easily performed (intra-abdominal rectum). Placement of presacral drains and washout of the distal rectal stump have been advocated for military wounds, but the role of such treatments in civilian injuries has not been well defined.[28]

Retroperitoneal Hematomas

The retroperitoneum is divided into 3 zones. Zone I is the central area bounded by kidneys, laterally extending from the diaphragm to bifurcation of aorta and inferior vena cava; zone II includes the lateral regions spanning from the kidneys to the paracolic gutters; and zone III is the pelvis below the aortic bifurcation. Penetrating injuries that cause hematomas in all regions should be explored. Zone I hematomas should always be explored in blunt trauma to rule out major vascular injury; however, zone II and III hematomas resulting from blunt trauma should not be explored unless the hematoma is expanding or pulsatile. Before exploring retroperitoneal hematomas, clinicians should prepare for possible excessive blood loss. Proximal and distal control of vasculature should be attempted prior to entering the hematoma; however, it is not always possible to achieve this control. The aorta may need to be clamped at the diaphragmatic hiatus or even intrathoracically if this is the only way to quickly attain control. As mentioned above, REBOA is another alternative to open aortic cross-clamping that is being used in some large centers. Vascular injuries are addressed by repair, grafting, temporary vascular stenting, or ligation, depending on the nature of the injury and the condition of the patient. Following penetrating abdominal trauma, all retroperitoneal hematomas warrant exploration.

Abdominal Compartment Syndrome

ACS is defined as a urinary bladder pressure greater than 25 mm Hg with progressive organ dysfunction that is improved after decompressive laparotomy. Elevated intra-abdominal pressure leads to abdominal distension, impediment of venous return, decreased cardiac output, and impaired end organ perfusion. The overall effect is renal, cardiac, and pulmonary compromise that ultimately leads to multiple organ dysfunction. Manifestations can be seen in all systems. Central nervous system signs present with elevated intracranial pressure secondary to obstructed jugular venous drainage. Cardiopulmonary complications include increased ventilatory pressures, decreased pulmonary compliance, poor oxygenation, and respiratory acidosis. Increased intrathoracic pressure causes

elevated filling pressures, decreased cardiac output, and increased systemic vascular resistance. Decreased perfusion leads to oliguria. Patients develop bowel wall edema leading to feeding intolerance, compromised intestinal barrier leading to translocation, and ileus. Venous congestion can result in lower extremity edema, and the patient is at increased risk for deep venous thrombosis and extremity compartment syndromes. The most common causes of ACS are uncontrolled intraperitoneal hemorrhage, ischemia-reperfusion injuries, and third spacing secondary to aggressive fluid resuscitation. The incidence of ACS after trauma has declined significantly, although it is still seen in acute care surgery patients who receive high-volume crystalloid resuscitation. A high suspicion for ACS should be maintained and bladder pressures serially measured. The treatment is decompressive laparotomy and temporary abdominal closure.[42,43]

TRAUMA TO THE PELVIS

Pelvic Fractures

Pelvic fractures can be a source of severe morbidity and mortality in trauma patients, and managing a hemodynamically unstable patient with pelvic fractures can be challenging. The key issues in management are identifying and controlling the source of bleeding and then thoroughly evaluating the surrounding pelvic and abdominal viscera for secondary injury. Unstable patients with known or suspected pelvic fractures require external compression devices, such as a sheet or towel wrapped and secured with towel clips or a commercially available device. A pelvic radiograph can make the diagnosis of pelvic fracture; however, a CT scan with IV contrast is the best diagnostic modality for evaluation of pelvic bleeding. CT should only be performed if the patient is stable. If a blush is seen on CT, and angioembolization is available in a timely fashion, it should be used to control arterial pelvic bleeding. If the patient is not hemodynamically stable, operative intervention (including pelvic packing or REBOA) is necessary. Pelvic bleeding can be notoriously difficult to control intraoperatively. If intra-abdominal bleeding or injury is not present and the patient remains unstable, preperitoneal packing is an option. Packs are placed directly into the paravesical space through a small suprapubic incision, which tamponades the bleeding. This method can also be used as an adjunct to laparotomy. External pelvic stabilization aids in hemorrhage control but is not a primary modality. Last, deployment of a REBOA catheter in zone 3 is now being studied as a rapid means of pelvic bleeding control until more definitive management is available. Once hemorrhage has been controlled and the patient

is stable, a comprehensive evaluation of the perineum, anus, rectum, genitalia, and genitourinary systems must be performed to evaluate for perforations or tears secondary to pelvic fractures.[44-46]

Genitourinary Injuries

Genitourinary injuries should be suspected according to the mechanism of injury, especially with pelvic fractures, gross hematuria, or microhematuria. FAST examination followed by CT scan is used to evaluate the extent of injury in hemodynamically stable patients, and CT has been shown to be more sensitive than IV pyelography.

Renal Injuries

Renal injuries are graded from I to V. Nonoperative management is the standard for most grade I to III injuries unless the patient is unstable. Operative intervention is necessary for instability, a hilar or pedicle injury, or excessive extravasation of blood or urine. Conservative management of injuries with devascularized segments is associated with higher rates of complications. Renal lacerations may be repaired; however, nephrectomy is the more common outcome. Prior to nephrectomy, the surgeon should verify the existence of a second kidney and in its absence pursue all practical attempts at repair. Traumatic renal arterial thrombosis is another well-known traumatic sequela that usually results in renal loss unless revascularization can be accomplished in less than 4 hours. Revascularization can be accomplished operatively or often with percutaneous thrombolysis or stenting.[47,48]

Bladder Injuries

CT cystography or conventional cystography should be used to evaluate bladder injuries. On CT scans without delayed cystography, free fluid is concerning for bladder injuries. Extraperitoneal injuries, which are much more common than intraperitoneal injuries, heal without operative intervention and can be managed with Foley catheter drainage. Intraperitoneal bladder injuries require operative intervention with double-layer repair using absorbable suture material as well as postoperative drainage. Ureteral injuries are rare and are more commonly seen in penetrating trauma.[47,48]

Urethral Injuries

Urethral injuries are most commonly seen with concomitant pelvic fractures and

are much more frequent in men than women. Clinical findings that should raise suspicion for urethral injuries include blood at the meatus, perineal ecchymosis, or a high-riding prostate on digital rectal examination. Additional clues include a palpably distended bladder with inability to void, difficulty with passing a Foley catheter, gross bleeding, and vaginal bleeding or lacerations. Passage of a Foley catheter does not exclude urethral injury. Diagnosis should be made via a retrograde urethrogram with a partially advanced catheter. The usual management of urethral injuries entails placing a suprapubic catheter and repairing the urethra in a delayed fashion.[47-49]

EXTREMITY AND PERIPHERAL VASCULAR INJURIES

Peripheral vascular injuries are more commonly found in penetrating rather than blunt trauma, but fractures and dislocations can injure vessels (ie, popliteal vascular injuries after knee dislocations). Arterial injuries are of greater concern and carry greater morbidity than venous injuries. Most arterial injuries require repair unless sufficient arterial flow can be demonstrated through tributaries. The majority of venous injuries may be ligated, although larger veins may be candidates for venorrhaphy. Lower extremity vascular injuries are much more common than upper extremity injuries. The most common types of arterial injuries include intimal tears, lacerations, transections, arteriovenous fistulas, arterial spasms, and traumatic aneurysms (true and pseudo). True aneurysms involve injury to the intima or to the intima and media with dilation of the vessel wall. False or pseudo-aneurysms involve full-thickness injury to the vessel with blood outside the lumen but contained within the surrounding tissue. Both usually require intervention. A high suspicion should always be maintained for vascular injury, and the *C* of the ABCDEs (circulation) involves evaluation of pulses in all 4 extremities. Hard signs of vascular injury are indications for operative intervention and include gross bleeding, expansile hematoma, a palpable thrill or bruit, and the 6 Ps: paralysis, pain, paresthesias, poikilothermia, pulselessness, and pallor. Soft signs of arterial injury include history of arterial bleeding prior to evaluation; proximity of a wound, fracture, or dislocation; nonpulsatile hematoma; and neurological injury or defect close to a major artery.[50,51]

Evaluation of injured extremities begins with palpation of the pulse or Doppler measurement of the arterial signal in an extremity. The pulse or signal should then be compared with the opposite extremity and should be equal. If there is disparity, or if suspicion exists, the clinician should determine the ankle brachial

index, which is the ratio of the Doppler arterial pressure of the injured extremity distal to the injury divided by the Doppler arterial pressure of an uninjured upper extremity. The ankle brachial index should be 0.9 or greater; if less, the injury requires further investigation. CTA and traditional angiography are comparable studies. Extravasation, occlusion, pseudo-aneurysm, and arteriovenous fistulas all require operative intervention.[52-55]

Extremity Compartment Syndromes

Compartment syndromes are caused by increased pressure within a contained tissue or fascial compartment. The collapsible veins become obstructed, leading to even greater compartment pressures that result in limited arterial inflow and eventual ischemia. Muscle ischemia can lead to irreversible damage due to tissue necrosis as well as nerve damage. The most common causes of compartment syndrome are vascular injury with ischemia and reperfusion, crush injuries, intramuscular hematomas, fractures, and combinations of orthopedic injuries with concomitant vascular compromise. Compartment syndrome is also well documented after excessive use of a muscle compartment, such as in athletes. The treatment for compartment syndrome is a fasciotomy, which allows the muscle compartments to expand without compromise of vascularity. Suspicion for compartment syndrome should arise with any extremity injury as outlined previously and especially with combined arterial and venous injuries. Additionally, if a vascular injury was sustained and reperfusion was established after more than 6 hours of ischemia, the patient is at very high risk for compartment syndrome and should undergo prophylactic fasciotomies. The clinical signs of compartment syndrome are tight, firm muscle compartments with pain on passive stretch, pain out of proportion to physical findings of the injury, and paresthesias. Paralysis and loss of pulse are late-presenting findings. The most common location for compartment syndrome is the calf, which has 4 fascial compartments. Numbness between the first and second toes on examination is pathognomonic for anterior compartment syndrome of the lower extremity. The forearm, thigh, and buttock are other potential areas of compartment syndrome, although the phenomenon can occur within any contained muscle group. Compartment pressures within the compartment of concern should be measured with an arterial line transducer device or a commercially available pressure-monitoring device. Compartment pressures 30 mm Hg or greater are diagnostic of compartment syndromes. Fasciotomies must be performed expeditiously for salvage of function and limb once the diagnosis is confirmed. Other complications that can occur include rhabdomyolysis, renal

failure, and infection due to necrotic muscle.[55,56]

TRAUMA AND HEMATOLOGY

Coagulopathy of Trauma

Acidosis, hypothermia, and dilution of coagulation factors have been recognized as important contributors to coagulopathy in severely injured patients. However, a significant number of patients present with coagulopathy, and this early coagulopathy is associated with a notable increase in mortality. Brohi and associates[57] demonstrated that shock induces coagulopathy. This traumatic coagulopathy is modulated through systemic activation of anticoagulant and fibrinolytic pathways. Hypoperfusion causes activation of thrombomodulin on endothelial cells, which then binds to circulating thrombin. This complex of thrombin-thrombomodulin induces an anticoagulant state through the activation of protein C. This complex also augments fibrinolysis by affecting the regulation of tissue plasminogen activator through the consumption of plasminogen activator inhibitor 1. The thrombin-thrombomodulin complex reduces the abundance of free thrombin, which limits the ability of thrombin to cleave fibrinogen to fibrin. This is evident in that these patients usually have normal levels of fibrinogen upon presentation.[57-60]

Damage Control Resuscitation

Damage control resuscitation involves preventing the lethal triad of coagulopathy, hypothermia, and acidosis rather than treating the sequelae. The primary transformation in resuscitation is through transfusion of blood products aimed at correcting the early coagulopathy. Multiple retrospective studies have demonstrated that the standard resuscitation practice of transfusing several liters of crystalloid prior to blood products worsens the initial coagulopathy of trauma and overall mortality. Additionally, giving a greater ratio of plasma and platelets to packed red blood cells has been shown to improve survival. A retrospective review of 17 leading civilian trauma centers demonstrated lower mortality and decreased hemorrhagic traumatic deaths when transfusion ratios of 1:1:1 were used. This has been followed by a prospective observation and, most recently, a prospective randomized trial, with consistent findings.[61-64]

Measurement of Coagulopathy: Thromboelastography

Standard methods of monitoring coagulopathy involve values captured from one moment in time, whereas clotting is a dynamic process. Thromboelastography was described in 1948 and is the only test of its kind that measures all steps of clot formation including strength and stability until eventual lysis. It is a new and emerging clinical tool for the treatment of coagulopathy. The strength of a clot is graphed over time as a characteristic elongated shape, the tracing of which entails 5 factors, each representing a character of the clot's development. (1) The period of time from the initiation of the test to the initial fibrin formation is labeled *R*. (2) The time from the beginning of clot formation until the amplitude of the thromboelastography reaches 20 mm, labeled *k*, represents clot formation. (3) The α-*angle*, which is the angle between the line in the middle of the tracing and the line tangential to the body, represents acceleration of fibrin buildup and cross-linking. (4) *MA* is the maximum amplitude that is the strength of the clot; it is dependent on platelet interaction with fibrin. (5) *MA60*, the rate of amplitude reduction 60 minutes after MA, represents stability. Each of these values can be used to evaluate the coagulopathy of a patient, and the individualized abnormalities can then be appropriately addressed through transfusion of platelets, plasma, or cryoprecipitate.[50,66]

Deep Venous Thrombosis

Trauma patients are at very high risk of developing a deep venous thrombosis (DVT) and eventual pulmonary embolism caused by the endothelial injury that occurs with trauma. In the absence of prophylaxis, patients with major or polytrauma have a greater than 50% chance of acquiring a DVT. Factors that have been independently associated with increased risk of DVT in trauma patients include extended hospital stay, increased duration of immobility, femoral venous line, venous repair, increasing age, need for operative intervention, lower extremity or pelvic fracture, and spinal cord injuries. Intermittent pneumatic compression devices should be applied upon admission in all patients. Low-molecular-weight heparin should be started in high-risk patients without a major contraindication. The timing in patients with contraindications has not been well studied and varies with the injury. Commonly identified injuries with bleeding risk upon admission include intracranial hemorrhage, incomplete spinal cord injury or a perispinal hematoma, solid organ injury, ongoing hemorrhage, or uncontrolled coagulopathy. Recent data suggest that chemical prophylaxis can safely be given to patients with intracranial hemorrhage within 24 hours of admission if the bleed is stable or the patient underwent a craniotomy. Standard dosing is usually 30 mg of low-

molecular-weight heparin every 12 hours, although this may need to be adjusted in the underweight or overweight patient. Patients with renal failure also require dosing adjustments. Anti–factor Xa levels can be used to help guide therapy. In patients with ongoing bleeding or other contraindications to prophylaxis, inferior vena cava filters, either permanent or removable, should be considered.[67]

SUMMARY

- Neurogenic shock: A type of shock (also called distributive shock) that usually occurs in patients with high thoracic or cervical spinal cord injuries. Autonomic dysregulation leads to hypotension, bradycardia, and usually dry warm extremities. Loss of sympathetic tone and unopposed parasympathetic output lead to vasodilatation and resultant hypotension. Patients also lose the sympathetic input required for reflex tachycardia.

- Massive hemothorax: Blood in the pleural cavity with chest tube output greater than 1,500 mL upon insertion or greater than 200 mL/h for 4 or more hours. This should prompt operative intervention.

- Cardiac tamponade: Compression of the heart secondary to buildup of fluid in the space between the pericardium and the myocardium. It classically presents as hypotension with muffled heart sounds, jugular venous distension, and pulsus paradoxus (inspiratory decrease in the systolic blood pressure of >10 mm Hg). FAST examination can be used to identify pericardial effusion in trauma patients.

- Thoracoabdominal stab wounds: Injuries below the level of the nipple. They carry the potential for diaphragmatic injury and therefore require some type of diagnostic study.

- Damage control laparotomy: Procedure performed in critically ill patients to limit operative time. Hemorrhage control is quickly controlled, and the patient is transported to the ICU for resuscitation. Definitive repairs, nonemergent interventions, and anastomoses are delayed until the patient is resuscitated and hemodynamically stable.

- Abdominal compartment syndrome: Condition characterized by elevated intra-abdominal pressure defined by a urinary bladder pressure greater than 25 mm Hg that leads to progressive organ dysfunction. The only therapeutic treatment is decompressive laparotomy.

- Ankle brachial index: Ratio of the Doppler arterial pressure of the injured extremity distal to the injury divided by the Doppler arterial pressure of an uninjured extremity. The ankle brachial index should be 0.9 or greater; if it is less than that, further investigation is required to evaluate for arterial injury.
- Central cord syndrome: Condition that presents with global sensory and motor deficits; the upper extremity function is affected more than the lower extremity function. This usually presents in patients with preexisting spondylosis after a hyperextension injury.

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CHAPTER 46

Critical Care Issues in the Postoperative Period

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Key words: postoperative, antibiotics, fluid therapy

Care of the postoperative patient must be approached in an organized, timely manner, with attention to the patient's dynamic physiological status. This need is magnified in ICU care. ICU patients must be cared for in a collaborative manner with the primary surgical service and any consultant services. In this population, the role of the intensivist is to act as a quarterback and incorporate all of the teams' game plans. Intensive care issues discussed in this chapter include fluid management, glycemic control, deep vein thrombosis, postoperative antibiotics, and the open abdomen.

FLUID MANAGEMENT

Postoperative fluid and electrolyte imbalances are associated with worsened outcomes. These imbalances may be a result of improper and varied prescription of fluids and electrolytes, which may be improved by the implementation of ICU protocols.

Fluids

The type, composition, and administration rate of postoperative IV fluid depend on the reason for prescription, alternative fluid sources, comorbidities, volume, and electrolyte status. IV fluids may be required for maintenance, replacement of losses, or resuscitation. Fluid types include crystalloids, colloids, and blood products.

Crystalloids

Crystalloids can be classified as isotonic, hypertonic, or hypotonic. Lactated Ringer's solution (LR) and 0.9% normal saline (NS) are the primary isotonic crystalloids. These differ in osmolarity and composition. NS has a higher osmolarity than LR—308 mOsm compared with 273 mOsm, respectively. NS contains 154 mEq/L of sodium and chloride each, whereas LR contains sodium, chloride, potassium, calcium, and lactate. NS is associated with a non-ion gap metabolic acidosis because of hyperchloremia; however, the clinical significance of this acidosis is unclear. Hypertonic saline (HS, 3%, 5%, and 7.5%) has been used to correct hyponatremia, reduce intracranial pressure in the treatment of traumatic brain injury, and resuscitate patients in shock or post trauma or burns. Animal models as well as in vitro and in vivo human studies have shown immunomodulatory and anti-inflammatory effects of HS. Hypotonic crystalloids include 0.45% NS with or without potassium chloride and/or dextrose. These are often used postoperatively for maintenance once volume status has been restored. Use of 0.45% NS after kidney transplant is well known, but there is no overwhelming evidence to support this practice over isotonic crystalloids.

Colloids

Colloids include the natural colloid, albumin (5% or 25% solution), and synthetic colloids such as dextrans, hetastarch, and gelatins. Because of the increase in oncotic pressure due to their molecular weight, colloids have long been touted as expanding intravascular volume more effectively than crystalloids. However, studies have shown that the ratio of crystalloid to colloid required for resuscitation is much less than previously believed, ranging from 1 to 2 rather than 1 to 4. Synthetic colloids are associated with risks such as anaphylactic reactions, renal failure, and coagulopathy. Moreover, hetastarch has been reported to be associated with increased mortality, particularly as the cumulative dose increases.

Maintenance Fluid Therapy

Traditional teaching is that immediately postoperatively, isotonic crystalloids should be used for maintenance and for replacement of any uncorrected perioperative losses such as from preoperative fasting or mechanical bowel preparation or from intraoperative third-space or blood loss. This adage is based on studies demonstrating increased salt and water retention and increased transcapillary leak of albumin after major surgery as well as decreased effective circulatory volume with anesthesia. Theoretically, isotonic crystalloids expand

the intravascular volume by one-third of the volume infused, although studies suggest that their effectiveness is less than originally believed. More recently, multiple randomized trials have compared the use of liberal versus restrictive fluid strategies on outcome after major surgery; however, interpretation of these trials is limited by differences in the terms used. A meta-analysis of 9 randomized trials in patients undergoing major elective abdominal surgery reclassified patients into 2 groups—those in a state of fluid balance and those in a state of imbalance. The study demonstrated a significant reduction in complications and length of stay among patients in a state of fluid balance.

Fluid Therapy for Resuscitation

All types of fluid have been used for resuscitating patients in shock—crystalloids, colloids, and blood products. Randomized trials and meta-analyses have compared isotonic crystalloids to hypertonic crystalloids and colloids, but no studies have demonstrated superiority of these alternative fluids.

Because of the potential to decrease edema and to favorably influence fluid balance, HS has been studied for resuscitation after trauma and burns. In particular, a meta-analysis found that HS is more effective than mannitol in treating elevated intracranial pressures. Prospective studies in burn patients suggest that HS may reduce fluid requirements within the first 24 hours post burn and decrease the risk of abdominal compartment syndrome (ACS). Despite potential benefits in reducing intra-abdominal and intracranial hypertension as well as overall fluid requirements, the effect of HS resuscitation in critically ill patients has not been fully evaluated, particularly with respect to potential harms. A multicenter randomized trial of prehospital administration of HS (with or without dextran) compared with NS in patients with hypovolemic traumatic shock was stopped early for futility and potential safety concerns. A subgroup of patients who received HS but no blood transfusions had increased mortality. Further adequately powered trials are necessary to determine whether HS is beneficial for resuscitation in specific subgroups of patients and whether the benefits balance the harms.

Colloids are more expensive, do not reduce mortality, and have significant side effects compared with crystalloids. Therefore, colloids are not recommended over isotonic crystalloids for the treatment of patients in shock. The 2016 international guidelines for the Surviving Sepsis Campaign recommend the use of crystalloids for initial fluid resuscitation in patients with septic shock or severe sepsis, with close monitoring of hemodynamic responsiveness to fluid

challenges. Since a multicenter randomized trial, the Saline versus Albumin Fluid Evaluation (SAFE) study, showed no difference in 28-day outcome in critically ill patients resuscitated with saline versus albumin, numerous randomized trials have compared crystalloid and colloid resuscitation. A recent update of a Cochrane review demonstrated no survival benefit to colloids compared with crystalloids for fluid resuscitation in patients after trauma, burns, or surgery.

Blood products are used in critically ill patients to correct coagulopathy, replace ongoing blood losses, and treat symptomatic anemia. Observational studies suggest that in trauma patients with hemorrhagic shock, early and aggressive empirical correction of coagulopathy with red blood cells, plasma, and platelets in a 1:1:1 ratio along with limitations on crystalloid infusion improves mortality. Further prospective and randomized trials are ongoing. In patients with septic shock, red blood cell transfusions have been used in early goal-directed therapy to improve oxygen delivery. However, red blood cell transfusions have not been demonstrated to improve outcome when used to increase oxygen delivery to supranormal levels. In the absence of shock, restrictive transfusion strategies are used in stable, asymptomatic anemic patients based on the Transfusion Requirements in Critical Care (TRICC) trial, which demonstrated no difference in mortality between restrictive and liberal transfusion strategies.

GLYCEMIC CONTROL

Pathophysiological Features of Perioperative Hyperglycemia

Both diabetes and acute hyperglycemia are risk factors for perioperative morbidity and mortality. Acute hyperglycemia is a common response to metabolic stress and critical illness. Perioperative hyperglycemia is influenced by patients' underlying glucose tolerance and the type and severity of disease. Release of the counterregulatory hormones glucagon, epinephrine, and cortisol augments hepatic production of glucose, particularly through gluconeogenesis. Insulin-mediated glucose uptake and glycogen synthesis in skeletal muscle are reduced as a result of a defect in the glucose transporter 4. Studies have cited the role of inflammatory cytokines as permissive to hyperglycemia.

Effects of Hyperglycemia

Acute hyperglycemia has multiple deleterious effects. It leads to dysregulation of

endothelial nitric oxide production with subsequent impairment of vascular reactivity. Key aspects of neutrophil function, including chemotaxis, phagocytosis, and the formation of reactive oxygen species, are also impaired. In turn, these changes lead to increased inflammation, vulnerability to infection, and multiple organ system dysfunction.

Intraoperative Glucose Control

The majority of data demonstrating a link between intraoperative glucose concentrations and adverse outcomes are from patients undergoing cardiac surgery. Observational studies have reported an association between intraoperative hyperglycemia in patients undergoing cardiac surgery and increased mortality. An association between strict intraoperative glucose control and decreased mortality with improved perioperative outcomes has also been reported in observational studies. In a retrospective, interventional study, 25 diabetic patients undergoing coronary artery bypass grafting and receiving subcutaneous insulin (target blood glucose <200 mg/dL) were compared with patients receiving continuous IV insulin infusion (target blood glucose changed over time). The results showed a 57% reduction in mortality in the patients receiving continuous insulin. However, this study was limited by heterogeneous study groups and the fact that the study was conducted over a 14-year period, during which changes in other clinical practices may have impacted the results. In summary, there is paucity of randomized controlled trials (RCTs) addressing intraoperative glucose management.

Postoperative Glucose Control

Several studies have evaluated the effects of hyperglycemia in the postoperative period, but most studies of postoperative glycemic control have been performed in patients undergoing cardiac surgery and in critically ill patients. Multiple retrospective studies have found an association between hyperglycemia and increased risk of wound infection in diabetic patients after cardiac as well as colorectal surgery and general surgery. However, a meta-analysis found insufficient evidence to support the use of tight glycemic control to prevent surgical site infections in adults.

Glucose Control in Critically Ill Patients

The first RCT on strict glycemic control (SGT) in surgical ICU—*Intensive*

Insulin Therapy in critically ill patients was performed at a single center. Target blood glucose 80 to 110 mg/dL was compared with conventional treatment (target blood glucose 180-200 mg/dL). Intensive insulin therapy was associated with a decrease in both ICU and in-hospital mortality. However, this study was unblinded, and a significant number of staff (1:1 nurse to patient ratio as well as study physician) were required to implement the insulin infusions. Furthermore, patients received IV glucose on arrival to the ICU, and an unquantified percentage of calories were administered via parenteral nutrition, with 60% of patients receiving combined parenteral-enteral feeding. Finally, the mortality of the control group was higher than expected for the severity of illness.

Subsequent RCTs failed to replicate the results of this initial study. A study performed by the same group in a medical ICU population using the same insulin protocol showed no mortality benefit, although in-hospital mortality was reduced in patients who stayed in the ICU for more than 3 days. Studies have thus failed to show mortality benefit with tight glycemic control.

Hypoglycemia

The consequences of hypoglycemia may be difficult to detect in the perioperative period. Signs of hypoglycemia may be masked, the compensatory response may be blunted, and patients may be unable to communicate their symptoms. It is thus imperative for ICU physicians to be wary of the development of hypoglycemia in all patients receiving insulin therapy. No current guidelines are available to help identify those patients at risk of developing clinically significant hypoglycemia.

Optimal Glucose Control

The optimal glycemic target for intraoperative and postoperative treatment is unknown, and the recommendations from various organizations regarding target glucose levels vary significantly. Generally, perioperative glucose less than 180 mg/dL is recommended (**Table 1**).

Table 1. Current Recommendations for Perioperative Glucose Control

Patient Setting	Society of Thoracic Surgeons	American College of Endocrinology	American Diabetes Association	Institute for Healthcare Improvement	American College of Physicians
Preoperative	<180 mg/dL	<140 mg/dL prior to meal, <180 mg/dL random	<140 mg/dL prior to meal, <180 mg/dL random	Not stated	Not stated

Intraoperative	<180 mg/dL	Not stated	Not stated	Not stated	Not stated
ICU	<180 mg/dL	140-180 mg/dL	140-180 mg/dL	<180 mg/dL	140-200 mg/dL

DEEP VEIN THROMBOSIS

Risk Factors for Venous Thromboembolism

Patients undergoing surgical procedures have an increased risk of developing thrombotic complications. In the past, the risk for deep vein thrombosis (DVT) in general surgery patients without thromboprophylaxis ranged from 15% to 30%, whereas the rates of fatal pulmonary embolus (PE) ranged from 0.2% to 0.9%. In surgical patients, the type of surgery is the main determinant of the risk of DVT—specifically, the type of surgery, the surgical site, and whether it is a minor or a major procedure. Other factors influencing risk of DVT in this population are outlined in **Table 2**. Risk of postoperative DVT is highest in the first 1 to 2 weeks following surgery, although venous thromboembolism (VTE) complications can occur later.

Table 2. Risk Factors for Venous Thromboembolism in General Surgery Patients

Type of surgery
Traditional risk factors Cancer Previous deep vein thrombosis Obesity Delayed mobilization
Age
Type of anesthesia
Duration of surgery
Postoperative infection

Methods of Thromboprophylaxis

Mechanical Methods

Mechanical methods of thromboprophylaxis, which include graduated compression stockings, intermittent pneumatic compression, and venous foot pump, act by increasing venous outflow or reducing stasis within the leg veins. The main benefit of mechanical prophylaxis is that it does not increase the risk of bleeding. Insufficient evidence is available to suggest that mechanical methods alone have significant effects on the rates of symptomatic VTE, PE, or mortality.

Pharmacological Methods

Studies have demonstrated that aspirin provides some protection against VTE. However, aspirin is less effective and has significantly increased risk of bleeding compared with other pharmacological agents. Heparins are the most widely recommended methods for thromboprophylaxis in general surgical patients. Unfractionated heparin (UFH) can be administered 2 hours prior to an operation, followed by postoperative administration 2 or 3 times daily. Multiple studies have demonstrated the therapeutic equivalence of low-molecular-weight heparin (LMWH) and UFH in prevention of VTE. However, LMWH has been shown to have both decreased and increased bleeding complications when compared with UFH. Bleeding rates with LMWH may be related to its dose. Benefits of LMWH over UFH for prophylaxis include once-daily dosing, no requirement for dose monitoring, lower risk of heparin-induced thrombocytopenia, and infrequent association with osteoporosis. Fondaparinux, a selective synthetic factor Xa inhibitor, has been tested in a surgical population and found to be as effective and safe as LMWH. In a double-blind randomized trial of patients undergoing major abdominal surgery, fondaparinux was found to be noninferior to LWMH for prevention of VTE and did not carry an increased risk of bleeding.

Recommendations for Venous Thromboembolism Prophylaxis

Recommendations for General Surgery

For general surgery patients, the intensity of prophylaxis of VTE should correspond to the estimated risk (**Table 3**). In general, thromboprophylaxis should continue until discharge from hospital. However, in patients undergoing major surgery for cancer or those with a history of VTE, continued prophylaxis for up to 28 days after hospital discharge should be considered.

Table 3. Recommendations for Venous Thromboembolism Prophylaxis in General Surgery Patients

Low risk (minor procedures, no additional risk factors for VTE)	Early and frequent ambulation
Moderate risk (major procedure for benign disease)	LMWH, UFH, or fondaparinux
High risk (major procedure for cancer)	LMWH, UFH 3 times daily, or fondaparinux
Very high risk (multiple risk factors for VTE)	LMWH, UFH 3 times daily, or fondaparinux combined with GCS and/or IPC
High risk of bleeding	GCS or IPC until bleeding risk decreases

Abbreviations: GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

Recommendations for Other Surgical Populations

Recommendations for VTE prophylaxis in other surgical populations are shown in **Table 4**. Routine thromboprophylaxis is recommended for patients undergoing bariatric surgery, although the optimal regimen, dosage, timing, and duration of thromboprophylaxis are unknown. The American College of Chest Physicians suggests using weight-adjusted prophylaxis in the morbidly obese patient. Trauma patients are at very high risk for development of VTE. Inferior vena cava filter is not recommended as prophylaxis, because it has not been proven to reduce the incidence of PE in this population and is associated with short- and long-term complications.

Table 4. Recommendations for Venous Thromboembolism in Specific Surgical Populations

Vascular surgery	
Without VTE risk factors	Early and frequent ambulation
With VTE risk factors	LMWH, UFH, or fondaparinux
Laparoscopic surgery	
Without VTE risk factors	Early and frequent ambulation
With VTE risk factors	LMWH, UFH, or fondaparinux
Bariatric surgery	LMWH, UFH 3 times daily, or fondaparinux with or without IPC

	devices
Thoracic surgery	LMWH, UFH, or fondaparinux GCS and/or IPC devices
CABG surgery	LMWH, UFH, GCS, or IPC devices
Trauma	LMWH with or without GCS or IPC devices

Abbreviations: CABG, coronary artery bypass graft; GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

Treatment of Venous Thromboembolism

In patients with confirmed acute postoperative DVT or PE, initial treatment should be with UFH, LMWH, or fondaparinux along with vitamin K antagonist initiated on the same day, with overlap of the 2 treatments for at least 5 days or until the international normalized ratio is 2 or higher for 24 hours. Oral anticoagulation therapy should be continued for 3 months or more with a target international normalized ratio between 2.0 and 3.0. Inferior vena cava filter for treatment of DVT is recommended only if anticoagulation is not possible because of risk of bleeding, and anticoagulant therapy should be started as soon as it is safe to do so. In patients with cancer, LMWH is recommended for the first 3 to 6 months of therapy, and anticoagulation with either LMWH or vitamin K antagonist should be continued until the cancer is resolved.

Surgical patients with PE and hemodynamic compromise are generally not candidates for thrombolytic therapy given the risk of bleeding. Pulmonary embolectomy may be an alternative if the appropriate expertise is available. Recommendations for VTE prophylaxis are dynamic, and current recommendations should be sought at all times.

POSTOPERATIVE ANTIBIOTICS

Postoperative patients may require critical care because of underlying comorbidities that predispose them to a difficult postoperative course or because of surgical complications and their consequences, such as anastomotic leak and subsequent multiple organ failure. Postoperative antibiotics can be categorized as prophylactic, empirical, or therapeutic. Multiple factors influence decisions regarding the spectrum and duration of antibiotics. Ultimately, the intensive care

provider must balance the risks of inadequate treatment or prevention of infection versus the harms and costs of inappropriate therapy and development of multidrug-resistant organisms.

Prophylactic Antibiotics

Surgical site infections (SSIs) are the second most common healthcare-associated infection and result in significantly increased length of hospital stay, ICU stay, readmissions, resource utilization, and mortality. The Surgical Care Improvement Project, which is a national quality improvement partnership to improve surgical care, advocates the appropriate timing and spectrum of prophylactic antibiotic administration to reduce SSIs. The Surgical Care Improvement Project also recommends limiting the duration of antibiotic prophylaxis to prevent the development of microbial resistance. For elective operations, prophylactic antibiotics should be discontinued within 24 hours after the end of the operation. The Surgical Care Improvement Project measures focus on common elective operations for which no controversy exists regarding antibiotic prophylaxis, such as vascular surgery, general abdominal colorectal surgery, initial hip and knee arthroplasty, abdominal and vaginal hysterectomy, and coronary artery bypass and other open-chest cardiac surgery except for transplant surgery.

Prophylactic antibiotic guidelines have been developed for trauma patients, the more severely injured of whom may require critical care. However, the paucity of high-quality evidence lends to controversy regarding the spectrum and duration of antibiotic prophylaxis. For example, although a Cochrane review of prophylactic antibiotics for penetrating abdominal trauma did not identify any high-quality trials for analysis, several guidelines recommend no more than 24 hours of antibiotic prophylaxis for penetrating abdominal injury if no hollow viscus injury is identified or if a hollow viscus injury is repaired within 12 hours of injury.

Empirical Antibiotics

Healthcare-associated infections significantly increase ICU and hospital length of stay and are associated with increased mortality when compared with similar community-acquired infections. Therefore, empirical antibiotic therapy is prescribed in the setting of presumed infection without a definitive diagnosis or identified organism. Empirical antibiotic therapy should be based on the likely causative agents given the patient’s history, comorbidities, prior infections,

clinical signs, and symptoms as well as the hospital's microbial epidemiological characteristics and patterns of susceptibility. Inadequate initial therapy (ie, antibiotics not directed at the causative organism) is associated with worsened outcomes. Initial empirical antibiotic therapy for patients with severe sepsis or septic shock should be initiated promptly, preferably after cultures are drawn; should be sufficiently broad; and should be adjusted for accompanying organ dysfunction. Care should be taken in using empirical combination therapy in patients with a predicted low risk of death as increased harms are associated with the use of such therapy in this population.

Daily reevaluation of empirical antibiotic therapy is recommended. The decision to continue therapy, stop antibiotics, or escalate or deescalate care should be based on clinical evidence of improvement and culture results, including susceptibilities. *De-escalation* refers to the strategy of narrowing the antibiotic spectrum or reducing the number of antibiotics based on positive cultures and stopping antibiotics in the setting of no identified infection. Although observational studies have identified a benefit to de-escalation, its efficacy and safety remain unproven as a recent Cochrane review did not identify any RCTs on the subject.

Therapeutic Antibiotics

Surgical interventions are often required to obtain source control of infections such as complicated soft tissue or necrotizing soft tissue infections and complicated intra-abdominal infections (eg, perforated diverticulitis, perforated appendicitis, or infected necrotizing pancreatitis). These patients are deemed to have established infections and therefore require therapeutic antibiotics for more than 24 hours postoperatively. Simple, uncomplicated infections such as nonperforated, nongangrenous acute appendicitis or a superficial abscess without significant cellulitis or signs of sepsis should respond to surgical therapy alone and do not require more than 24 hours of antibiotics. Other intra-abdominal infections that do not require more than 24 hours of postoperative antibiotics include (1) gastric or proximal small bowel perforations for which source control is achieved within 24 hours, (2) traumatic bowel injuries repaired within 12 hours and/or with intraoperative contamination with bowel contents, (3) uncomplicated acute appendicitis (no perforation, abscess, or local peritonitis), and (4) severe necrotizing pancreatitis without a diagnosis of infection.

Often, initial antibiotic therapy is empirical given that definitive diagnosis may be determined intraoperatively; therefore, appropriate antibiotics should be

initiated preoperatively. Antibiotic spectrum should be determined by the presumed cause of infection and likely associated pathogens as well as the factors mentioned previously. The use of culture results to modify treatment, particularly in the setting of appropriate clinical response and the presence of untreated or resistant organisms, is controversial. The duration of therapeutic antibiotics is determined by the adequacy of source control, severity of disease, and clinical response of the patient. For patients with intra-abdominal infections, a combination of clinical resolution of the infection, normalization of the white blood cell count, lack of fevers, and resumption of oral intake has been used to stop antibiotic therapy with a low rate of failure. Most recently, the Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection (STOP-IT) showed the adequacy of an approximately 4-day duration of antibiotics after source control for intra-abdominal infections.

The need for prolonged antibiotic therapy beyond a week based on persistent leukocytosis, fevers, or failure of the infection to resolve typically indicates treatment failure. Patients who fail to exhibit improvement after surgical intervention and appropriate antibiotic administration should undergo additional diagnostic evaluation for inadequate source control and the need for further surgical intervention.

THE OPEN ABDOMEN

The use of the open abdomen in the management of surgical emergencies continues to evolve. Prior to 1980, patients with severe abdominal trauma requiring emergent surgery were managed with one definitive procedure. Such operations (especially if for significant intra-abdominal hemorrhage) occasionally resulted in death secondary to the “bloody vicious cycle” (also known as the “lethal triad”), which encompasses acidosis, hypothermia, and coagulopathy. Appreciating that this cycle must be interrupted, the “bailout” approach in which an abbreviated operation was performed and the patient was left with an open abdomen was described. Subsequently, this approach was refined with the plan being to return to the operating suite after all of the physiological derangements have been corrected. The investigators coined this a “damage-control” laparotomy. This technique is now used in other surgical fields, including general surgery and vascular surgery.

The overall management of the open abdomen is complex and requires an experienced team. The phases include the preoperative period, the initial operation, the initial postoperative period in the ICU, the subsequent operations,

and the definitive closure of the abdomen. The initial postoperative period in the ICU is discussed further here. The critical management issues during this period include correction of physiological abnormalities, monitoring for ACS, nutritional supplementation, and the use of antibiotics.

Correction of Physiological Abnormalities

The immediate goal following initial damage control surgery is the correction of physiological abnormalities, including volume resuscitation and hemodynamic stabilization, correction of hypothermia, and correction of coagulopathy. Using this plan, one can reverse the lethal triad and ready the patient for a return to the operating suite for reexploration.

Volume Resuscitation and Hemodynamic Stabilization

At the center of this therapy is volume resuscitation (and hemodynamic stabilization) via the aggressive infusion of crystalloids, colloids and blood products. Fluid management strategies, as discussed earlier in this chapter, are not reviewed further here. The adequacy of resuscitation is clinically monitored by observing vital signs and urinary output. As such, other end points of resuscitation have been identified, including central venous pressure, lactate levels, and base deficit. More information on end points of resuscitation can be found in **Chapter 10**.

If the patient does not respond appropriately to volume resuscitation, vasopressors and inotropes should be considered. The goal for vasopressor therapy is maintenance of a mean arterial pressure 65 mm Hg or more in adequately resuscitated patients. The use of pulmonary artery catheters in this population should be individualized, and they should be used primarily when clarification is required.

Correction of Hypothermia

Hypothermia is not uncommon following damage control surgery (and the open abdomen). Hypothermia commences with the initial insult (eg, trauma, perforated viscus) and is exacerbated by reduced perfusion, prolonged exposure, volume resuscitation, and interventional procedures. As part of the lethal triad, hypothermia must be prevented through multiple strategies or corrected in this patient population. First and foremost, the patient should be kept dry to reduce evaporative heat loss. The patient should be covered or insulated to reduce

convection, conduction, and radiant heat loss. If feasible, the ICU room temperature should be maintained higher than 28°C (82.4°F).

The remaining options are considered active warming and can be either external or internal. External warming mechanisms include forced air warming devices, warm water blankets, and radiant heaters, all of which are commonly used. The internal options range in their invasiveness. Cold IV fluids will quickly result in hypothermia. As such, all fluids administered should be warm. If large volumes are required, high-capacity fluid warmers should be used. They have been shown to improve resuscitation in major trauma, decrease requirements for fluid and blood, lessen coagulopathy, decrease the time to correction of hypothermia and acidosis, and decrease complications in comparison to standard therapy. For patients requiring mechanical ventilation, the gases should be humidified and warmed. With severe hypothermia (temperature <33°C [91.4°F]), more invasive and aggressive rewarming options should be considered, including lavage (gastric, bladder, peritoneal, and/or pleural) and extracorporeal rewarming. The fact that normal coagulation may not be achievable until the core temperature reaches 34°C (93.2°F) (even in light of appropriate factor replacement) supports these options despite their invasiveness.

Correction of Coagulopathy

The incidence of coagulation abnormalities following damage control surgery (and with an open abdomen) is high. The etiology of coagulopathy is multifactorial – hypothermia, acidosis, clotting factor dilution, and electrolyte abnormalities are some of the causes. Conventional laboratory assessments of coagulation have limitations in situations involving damage control surgery; therefore, other assessment tools such as thromboelastography and activated coagulation time should be considered. No simple algorithm is available for the correction of coagulopathy in this patient population. This topic is discussed in much greater detail in **Chapter 31**.

Monitoring for Abdominal Compartment Syndrome

In the immediate post-surgical period, critically ill patients with or without an open abdomen should be monitored for the development of ACS via bladder pressure monitoring. ACS is defined as a sustained intra-abdominal pressure greater than 20 mm Hg associated with new organ dysfunction or failure. Risk factors are many, including shock and aggressive fluid resuscitation. Despite this definition, the diagnosis primarily remains a clinical one and requires a high

index of suspicion. Suspicious signs include increased ventilator inspiratory pressures, oliguria progressing to anuria, decreased cardiac output and hypotension, and increased intracranial pressures. If ACS is suspected, a decompressive laparotomy (or removal of the temporary abdominal closure) should be performed. This can be performed in the ICU or the operating suite.

Nutritional Supplementation

Nutritional support should be implemented once the patient is resuscitated. Studies have documented the safety of feeding patients with an intact gastrointestinal tract and an open abdomen. Many of these patients possess normal gut integrity and tolerate enteral nutrition. We recommend use of the American Society for Parenteral and Enteral Nutrition Clinical Guidelines in prescribing enteral nutrition.

Benefits of enteral nutritional support include decreased time to abdominal fascial closure, decreased fistula rate, decreased pneumonia rate, and consequently decreased overall hospital costs. In patients with the gastrointestinal tract left in discontinuity, full enteral feeds should be held until continuity is reestablished. Nasal tubes are preferred over the use of transabdominal feeding tubes secondary to the risk of fistulas and wound closure complications.

Use of Antibiotics

The use of antibiotics depends on the presence of contamination or infection. In the absence of either, the use of prophylactic antibiotics is neither supported nor refuted. When prophylaxis is undertaken in these cases, administration for more than 24 hours is not supported by the literature. In instances of contamination or infection, empirical antibiotics should be initiated. Secondary to the vast array of potential species of contamination, the spectrum of coverage should be broad. The optimal duration of antibiotics in these cases has yet to be determined. The clinical course and culture data of the patient should be monitored. Based on these parameters, the antibiotics should be adjusted as previously discussed in this chapter.

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CHAPTER 47

Obstetric Critical Care

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Key words: amniotic fluid embolism, acute respiratory distress syndrome, cardiogenic shock, preeclampsia, posterior reversible encephalopathy syndrome, venous thromboembolism, septic shock, postpartum hemorrhage, placental abruption, cardiomyopathy, maternal cardiac arrest

Pregnancy causes important physiological changes that affect the spectrum of critical illness in pregnant patients. Management of pregnant patients requires consideration of the fetus, which can be harmed by interventions intended to benefit the mother. Collaboration between intensivists, obstetricians, anesthesiologists, and neonatologists will produce the best possible outcome for a critically ill pregnant patient.

PHYSIOLOGICAL CHANGES OF PREGNANCY

Circulatory Changes

During pregnancy, maternal circulation transforms to meet the metabolic demands of both the mother and fetus through increased vascular volume, venous return, cardiac output, and oxygen delivery. These normal physiological changes are caused by hormonal effects from the corpus luteum of pregnancy and the placenta. As the gravid uterus grows, it adds parallel arterial and venous circuits to the circulation, which expand the circulating volume and decrease the systemic vascular resistance. As systemic vascular resistance decreases, blood pressure declines during pregnancy, remaining at its nadir from 16 to 28 weeks.

Although cardiac output increases, pulmonary artery and capillary wedge

pressures remain within the range considered normal for nonpregnant patients. An enlargement of the cardiac silhouette on chest radiograph and the appearance of a physiological third heart sound are due to the normal increase in circulating volume. Decreases in serum albumin concentrations lead to decreased colloid osmotic pressure, which, in addition to increased aldosterone, causes peripheral edema.

As the gravid uterus grows, it can compress the inferior vena cava, leading to a clinically important decrease in venous return, cardiac output, and blood pressure. This phenomenon becomes increasingly problematic near term, especially when the patient is positioned supine, and is the reason that the left lateral decubitus position and left lateral displacement of the uterus are regarded as critical maneuvers in resuscitation of the hypotensive pregnant patient to maintain adequate uteroplacental perfusion.

Respiratory Changes

The changes in respiratory function are driven by the metabolic consequences of the enlarging fetus and placenta and the mechanical effects of their expansion on the respiratory system. Oxygen consumption increases, carbon dioxide production increases, and the gravid uterus displaces the diaphragm cephalad, resulting in a 10-25% decrease in functional residual capacity.

During pregnancy, increasing levels of progesterone increase minute ventilation, primarily via an increase in tidal volume, causing a respiratory alkalosis. Renal compensation results in an arterial pH that is only slightly alkalemic. Thus, the normal arterial blood gas in pregnancy includes a P_{CO_2} in the range of 27 to 32 mm Hg, pH in the range of 7.40 to 7.45, serum bicarbonate in the range of 18 to 21 mEq/L, and P_{O_2} in the range of 98 to 101 mm Hg.

Clinically, the increased oxygen consumption and decreased functional residual capacity synergistically produce more rapid desaturation during episodes of hypoventilation and apnea.

Renal and Gastrointestinal Adaptations

Renal blood flow increases during the first and second trimesters and declines toward normal in the third trimester. Glomerular filtration increases from 12 to 16 weeks, reaching its peak of 50% above baseline, and remains elevated throughout the remainder of pregnancy. Together, these changes reduce serum

creatinine compared with non-pregnant levels, typically to the range of 0.5 to 0.7 mg/dL. Levels of serum creatinine in the normal range likely indicate renal dysfunction.

Lower esophageal sphincter tone is decreased throughout pregnancy, primarily due to the effects of progesterone. The gravid uterus compresses all of the contents of the peritoneum, including the stomach. Overall, gastrointestinal motility is reduced during pregnancy, most likely from a combination of this mechanical impingement and hormonal effects. Although gastric emptying is prolonged, basal gastric acid secretion and pH are unchanged by pregnancy.

Fetal Oxygen Delivery

The placenta is a concurrent-flow oxygen exchange membrane. Oxygen delivery to the placenta is determined by hemoglobin, hemoglobin saturation, and blood flow. Because the uterine vasculature is maximally dilated throughout pregnancy, the principle determinant of uterine blood flow is arterial pressure. The increased flow associated with the vasodilation of pregnancy more than compensates for a relative anemia. Hypotension is clinically the most important cause of decreased oxygen delivery to the placenta and fetus. Because fetal hemoglobin is avid for oxygen relative to adult hemoglobin, maternal P_{O_2} is less important as a determinant of fetal oxygen delivery.

Following are key concepts regarding physiological changes of pregnancy and placental oxygen delivery:

1. Pregnancy accounts for the baseline hyperdynamic circulation. Active labor, fever, major injury, and infection can require further increases in cardiac output and placental oxygen delivery.

2. Hypotension is more threatening to fetal well-being than is hypoxia. Hypotension in conjunction with anemia or hypoxia is more deleterious than hypotension alone. Uteroplacental flow is pressure dependent and is not autoregulated.

3. Oxygen delivery to the placenta is best defended by maintaining a normal circulating volume, adequate hemoglobin, and adequate cardiac output. Positioning the patient in the left lateral decubitus position or displacing the uterus to the left can dramatically improve venous return, cardiac output, and blood pressure. The administration of supplemental oxygen is always

appropriate in hypoxic circumstances.

4. Fetal monitoring should be performed in the presence of a viable fetus. Fetal heart rate monitoring is recommended to assess fetal well-being. This usually requires a nurse with specialized training in obstetrics and the active collaboration of the obstetric team. In most instances, adequate resuscitation of the mother will suffice to resuscitate the fetus. Supplies for an emergent bedside cesarean delivery along with fetal resuscitation equipment should be at the bedside of every critically ill pregnant patient with a viable fetus.

5. Delivery of the fetus can dramatically simplify the management of a critically ill pregnant patient, as it reduces uterine obstruction of venous return and removes the fetus from the harms associated with maternal hypotension, hypoxia, and therapeutic interventions.

Critical Illness and Mortality in Pregnancy

Recent data about ICU care of obstetric patients and maternal mortality suggest that the distribution of diagnoses has changed substantially over the past few decades. No one diagnosis or category of diagnoses represents a majority of admissions. Preeclampsia, hemorrhage, and sepsis remain the primary indications for ICU admission.The National Partnership for Maternal Safety has proposed the Maternal Early Warning Systems which calls for physician bedside assessment of the parturient to facilitate early recognition of abnormal vital signs (heart rate < 50 or > 120, diastolic blood pressure > 100, systolic blood pressure < 90 or > 160, respiratory rate < 10 or > 30, oxygen saturation on room air < 95%, oliguria </= 35cc/hr for > 2 hrs, and maternal agitation, confusion or unconsciousness), diagnosis, and acceleration of treatment for pregnant women who become critically ill.

Circulatory Disorders of Pregnancy

The initial approach to the gravida in shock distinguishes the vasodilated shock of sepsis from the numerous causes of low cardiac output, including hypovolemia and cardiac dysfunction. Focused cardiac ultrasound conducted using bedside transthoracic echocardiography has supplanted the pulmonary artery catheter in the assessment of shock of indeterminate cause and can diagnose cardiomyopathy, valvular dysfunction, right ventricular shock, regional wall motion abnormalities from myocardial infarction, and aortic dissection.

Internal jugular and subclavian insertion sites are strongly preferable to femoral insertion for central line placement in gravid patients.

The management of unstable cardiac rhythms in pregnant patients is complicated by the fact that amiodarone is contraindicated. Adenosine, lidocaine, quinidine, and procainamide may all be used with relative safety, as can β-blockers after the first trimester. Updated guidelines to manage maternal cardiac arrest were published by the American Heart Association in 2015. If return of spontaneous circulation does not occur, bedside perimortem cesarean delivery should start 4 minutes into the resuscitation if the fetus is more than 20 weeks gestation or if the uterus appears gravid (may be at earlier gestation).

Hemorrhagic Shock

Hemorrhage is a leading cause of ICU admission and death in pregnancy. Examples of prepartum causes include ectopic pregnancy, abortion, placenta previa, abruption, and trauma; postpartum causes include uterine atony, rupture, inversion, abnormal placentation, retained placenta, and surgical trauma.

Placental abruption occurs most commonly in patients with hypertension, high parity, cocaine abuse, tobacco abuse, and previous abruption. Patients typically present with painful vaginal bleeding that can be mistaken for labor. Diagnosis is made with ultrasound, which reveals the source of bleeding to be intrauterine. Maternal complications include acute renal failure and disseminated intravascular coagulation (DIC), and maternal death occurs in up to 5% of cases.

Hemorrhage due to placenta previa has declined because of early ultrasound identification of this condition, which affords altered strategy of delivery. In those rare instances where the diagnosis has not been established prior to the onset of labor, vaginal examination can cause massive hemorrhage.

Uterine rupture can occur in the multiparous patient with protracted labor, in trials of vaginal birth after cesarean delivery, and with use of uterotonic agents. Because rupture happens during labor, the pain that rupture produces is often mistaken for labor pain. Peritoneal signs may be present. The laboring patient can exsanguinate into the gravid abdomen with little clinical indication that this is the cause of shock. Rupture into the bladder typically causes hematuria; the onset of hematuria and increased abdominal pain in a laboring patient should trigger an evaluation for uterine rupture.

The incidence of uterine atony, which is the most common cause of postpartum

hemorrhage, has increased over the past 10 years. Uterine atony is associated with prolonged labor, multiple gestation, polyhydramnios, abruptio placentae, oxytocin administration, retained placenta, and chorioamnionitis. Uterine atony is treated with uterine massage, oxytocin, and, in more severe cases, methylergonovine and prostaglandin analogs such as carboprost tromethamine. Methylergonovine is associated with nausea, diarrhea, hypertension, and cerebral hemorrhage, whereas prostaglandin analogs are associated with nausea, diarrhea, and bronchospasm.

Other causes of postpartum hemorrhage include surgical trauma, uterine inversion, retained placenta, and amniotic fluid embolism (AFE). Surgical hemorrhage can be caused by lacerations from instruments used for delivery, including the incision in the uterus for cesarean delivery. Balloon tamponade, compression sutures, and embolization are conservative measures used to control postpartum bleeding; open surgical interventions such as exploration, arterial ligation, and hysterectomy are reserved for the most severe or refractory cases.

Trauma remains an important cause of nonobstetric hemorrhage. Motor vehicle accidents, falls, and assaults can cause internal bleeding, hypovolemia, and shock. The gravid woman is at increased risk of hemorrhage from blunt trauma because blood flow to the entire pelvis is increased. Traumatic injuries that are unique to pregnancy include amniotic membrane rupture, placental abruption, uterine rupture, premature labor, and fetal trauma. Rapid deceleration can sheer the relatively rigid placenta off the relatively elastic uterus, causing placental abruption, which complicates 20% to 40% of major injuries. Abdominal pain and vaginal bleeding should trigger an obstetric ultrasound in any pregnant patient who has sustained a deceleration injury. Heavy bleeding should prompt evaluation for DIC. Penetrating trauma of the abdomen in pregnant patients is likely to cause critical injury due to the presence of the pregnant uterus and fetus, given that the remainder of the abdominal contents are compressed into the small volume cephalad to the uterus.

The management of hemorrhagic shock in the pregnant patient is similar to its management in other settings (eg, large-bore access, serial laboratory hemorrhage panels including hemoglobin levels and coagulation studies, and resuscitation with blood products). Fetal monitoring is indicated, as are left lateral displacement of the uterus, the administration of supplemental oxygen, and early volume resuscitation. The normal physiological state of pregnancy may conceal a developing pathological condition, and a high index of suspicion is prudent for seemingly subtle changes in vital signs and in all cases of trauma.

Because of the explosive nature of obstetric hemorrhage, transfusion with type-specific or O-negative blood may be required. In obstetrics, unlike other settings, even moderate hemorrhage is likely to be associated with the onset of DIC. Measurement of factor VIII levels may be useful in the diagnosis of DIC. Fibrinogen levels are twice as high in pregnancy as in the normal population (the normal value is 400 mg/dL in pregnancy). Fibrinogen that approaches 200 mg/dL in pregnancy has been found to be an independent predictor of severe postpartum hemorrhage. Correction of hypofibrinogenemia in the bleeding patient with a consumptive coagulopathy may be achieved with plasma or more effectively with cryoprecipitate. Massive hemorrhage also can cause a coagulopathy from dilutional thrombocytopenia, which manifests at platelet counts of 65,000 to 85,000 per mm^3. When obstetric hemorrhage occurs, activation of a massive transfusion protocol and communication with the blood bank are crucial to quickly obtain adequate blood product supplies for the patient.

Septic Shock

Sepsis and septic shock are the causes of approximately one-quarter of all ICU admissions and 10% of all deaths in pregnant patients.The diagnosis of sepsis is made more difficult by the vasodilated, hyperdynamic circulation normally present in the gravid patient. Some of the most common causes of obstetric sepsis include postpartum endometritis, chorioamnionitis, septic pelvic thrombophlebitis, septic abortion, and pyelonephritis. Causes of non-obstetric sepsis include appendicitis, cholecystitis, and pneumonia. Other causes of sepsis are procedure related (wound infection, amniocentisis). Sepsis occurs most commonly in the postpartum period and occurs more frequently in patients with prolonged rupture of the membranes, cesarean section, or other operative interventions.

The most common cause of sepsis is endometritis, which presents with fever, abdominal pain and tenderness, and purulent lochia. Episiotomy sites and surgical incisions are less commonly the sources of infection. Chorioamnionitis complicates up to 1% of all pregnancies and is another of the most common causes of sepsis in pregnancy. Risk factors include prolonged rupture of membranes and prolonged labor, but chorioamnionitis can also occur as a complication of amniocentesis, cervical cerclage, or maternal bacteremia. Fever, maternal and fetal tachycardia, uterine tenderness, and foul-smelling amniotic fluid are typically present.

Evaluation and management of the obstetric patient with sepsis should take into account the additional sources of infection and different spectrums of causative organisms during pregnancy. The genitourinary tract requires appropriate cultures and careful evaluation, which might include renal ultrasound, computed tomography (CT) or ultrasound evaluation of the appendix, and ultrasound and appropriate cultures of the uterus and placental tissues. Because many infections are polymicrobial, broad-spectrum coverage (absent an identified organism) for gram-positive, gram-negative, and anaerobic organisms is usually indicated. Delivery of the placenta is the definitive treatment for chorioamnionitis; antibiotic therapy alone is unlikely to resolve the infection.

No randomized prospective studies are available to guide recommendations for the management of septic shock in pregnant patients. It is reasonable to use early goal-directed therapy, with the understanding that volume infusion is preferable to therapy with vasoconstrictors in the resuscitation of these patients. The selection of vasoactive drugs is best left to the judgment of the critical care team caring for the patient. Other measures, including steroid replacement, have not been systematically evaluated in pregnant or peripartum patients. It is reasonable to commence treatment with steroid replacement in patients with septic shock refractory to volume resuscitation and support with a vasoactive agent.

Cardiogenic Shock

In most instances, shock from cardiac dysfunction in the pregnant patient is caused by exacerbation of preexisting disease. In many instances, previously subclinical disease (often valvular disease or pulmonary hypertension) is unmasked by the physiological demands of pregnancy.

Predictors of increased maternal morbidity include New York Heart Association class III or IV symptoms, cyanosis, mitral or aortic stenosis, and left ventricular systolic dysfunction. Patients with Eisenmenger physiology, cyanotic congenital heart disease, and pulmonary hypertension have the highest peripartum mortality.

Peripartum cardiomyopathy occurs in 1 in 1,300 to 4,000 pregnancies and can present between 1 month antepartum and up to 6 months postpartum. Risk factors include African American race, older age, multiple gestations, multiparity, anemia, preeclampsia, and postpartum hypertension.

Other cardiac complications of pregnancy include endocarditis, myocardial

infarction, and aortic dissection. Endocarditis typically occurs in association with underlying valvular disease; in patients with otherwise normal heart valves, endocarditis is generally associated with IV drug abuse. Myocardial infarction historically has been uncommon in pregnancy but has become more common with parturients of advanced maternal age. Some of this increase in incidence may be the sequela of coronary artery dissection. The risk of aortic dissection is increased in pregnancy, especially in the third trimester. When serum markers of myocardial ischemia are negative and echocardiography is nondiagnostic, a CT scan or magnetic resonance imaging may be warranted to evaluate for aortic dissection. Evaluation of the volume status of pregnant patients is often challenging because central venous pressure measurements and dynamic parameters may be unreliable. Echocardiography may be the most useful bedside tool to assess the adequacy of the circulating volume.

In patients with cardiogenic shock, dobutamine is the drug of choice to support circulation. When afterload reduction is indicated in the ICU setting, IV labetalol is typically used. Intravenous nitroprusside and nitroglycerin should be regarded as second-line agents. In less acute settings, labetalol or hydralazine should be used, as there is substantial experience with both agents in the obstetric population relative to all of their alternatives. Angiotensin-converting enzyme inhibitors are absolutely contraindicated as they can cause fetal growth retardation, oligohydramnios, anuric renal failure, and congenital fetal malformations. Maternal mortality is high in patients who deliver within 2 weeks of infarction; hence, infarction is one instance in which postponing delivery may be advantageous. Metabolic disturbances can worsen cardiac function; hypocalcemia, hypophosphatemia, acidosis, and hypoxemia require aggressive correction. In patients with refractory cardiogenic shock, extracorporeal membrane oxygenation or placement of a left ventricular device may be considered.

Labor is especially dangerous for parturients with cardiogenic shock or congestive heart failure. Vaginal delivery in the left lateral decubitus position is preferable. Epidural anesthesia attenuates the sympathetic response to the pain of uterine contractions but can also cause hypotension from venodilation in some patients, which is treatable with a phenylephrine infusion. Cesarean delivery should be reserved for patients who have other obstetric complications or in instances where fetal distress warrants the additional risk of the operation and its obligatory blood loss.

Preeclampsia

Preeclampsia is thought to result from abnormal placental implantation with altered production of angiogenic factors causing disruption of the maternal vascular endothelium in multiple organ systems. This leads to hypertension associated with thrombocytopenia, impaired renal or liver function, headache, and/or pulmonary edema. In 2013, the American Congress of Obstetricians and Gynecologists published an executive summary on hypertension in pregnancy; according to this publication, proteinuria is no longer required to diagnose preeclampsia.The timing of disease onset ranges from the 20th week of pregnancy through the postpartum period. Preeclampsia occurs in 3% to 5% of pregnant women and up to 7.5% of first pregnancies. Risk factors include chronic hypertension and renal disease, diabetes mellitus, obesity, age 40 years or older, and thrombophilia. Multiple gestation and hydatidiform mole are also risk factors, as is a history of preeclampsia in prior pregnancy or in a first-degree relative. Eclampsia is defined by seizures, which increase the risk of poor outcome for the mother and fetus. Seizures may occur up to 1 month postpartum and may not be preceded by overt preeclampsia. Posterior reversible encephalopathy syndrome caused by vasogenic cerebral edema may be a consequence of eclampsia.

Management depends on severity, and delivery of the placenta is the only curative therapy. Blood pressure control may prevent end organ damage but does not affect progression to eclampsia. The goal of therapy in preeclampsia is a well-timed delivery to maximize both maternal and fetal well-being. Early in gestation, delivery may be postponed if the disease is mild and the patient is carefully observed. Blood pressure is controlled with either labetalol or hydralazine. Magnesium sulfate halves eclampsia risk in patients with preeclampsia and likely reduces the risk of maternal death. Numerous clinical trials have demonstrated the benefit of magnesium sulfate in preventing eclamptic seizures as well as their recurrence, and this agent is superior to diazepam, phenytoin, and nimodipine.

A lethal variant of preeclampsia is HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes, and low platelet counts. The differential diagnosis includes fatty liver of pregnancy and, when renal dysfunction is also present, hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. These latter entities require plasmapheresis for treatment, whereas the HELLP syndrome requires emergent delivery to prevent life-threatening thrombocytopenia or hemolysis.

Respiratory Disorders of Pregnancy

Respiratory failure requiring admission to the ICU is most often the result of acute hypoxic respiratory failure, including aspiration, pneumonia, thromboembolic disease, AFE, or venous air embolism. As reviewed below, management of mechanical ventilation in the pregnant patient must account for the changes in gas exchange and chest wall mechanics associated with pregnancy.

Aspiration

Aspiration risk increases throughout pregnancy. Causes include pregnancy-associated reduction in gastric emptying, decreased lower esophageal sphincter tone, and increased intragastric pressure caused by the extrinsic compression of the gravid uterus. Aspiration risk is greatest when the patient is under the influence of sedative hypnotics or anesthetic agents, and in such situations all pregnant patients after their 20th week of pregnancy are treated as if they have a full stomach. Aspiration precautions earlier in pregnancy may be prudent given increased circulating progesterone in the first trimester as well as due to gastrin secretion and emergence of the uterus from the pelvis, which can cause cephalad displacement of the stomach in the second trimester.

Avoiding aspiration is a high priority in airway management of the pregnant patient. Tracheal intubation following administration of an oral nonparticulate antacid (sodium citrate) is accomplished via rapid sequence induction using cricoid pressure or with an awake technique. The larger the volume of aspirate, and/or the more particulate or acidic it is, the worse the ensuing chemical pneumonitis will be. Acute respiratory distress syndrome (ARDS) can develop as a complication. The role of antibiotics remains controversial; no evidence is available to show that corticosteroids are of any benefit in simple aspiration. Antibiotic therapy is appropriate for patients who develop signs of a complicating bacterial pneumonia.

Tocolytic Therapy

Tocolysis with β-agonists for preterm labor causes pulmonary edema in approximately 4% of patients. Tocolysis-associated pulmonary edema most often presents during the time of drug administration but can occur as late 12 hours postpartum or 24 hours after administration. Risk factors include multiple gestations, concurrent infection, and treatment with corticosteroids.

Clinically, patients present with dyspnea, chest discomfort, tachypnea, and tachycardia. The differential diagnosis includes pulmonary embolism (PE), aspiration, pneumonia, air embolism, and AFE. Physical examination and chest radiography reveal signs of pulmonary edema. Focal infiltrates on chest radiography will support the diagnosis of aspiration or pneumonia; a paucity of infiltrates should increase suspicion of PE. In most instances, patients experience dramatic improvement with discontinuation of tocolysis, oxygen administration, and diuresis. In those rare instances when a patient is admitted to the ICU with the diagnosis of tocolysis-induced pulmonary edema, a search for other causes or aggravating factors (eg, infection, valvular disease or cardiomyopathy) is prudent.

Pneumonia

Despite the altered immunity present in pregnant patients, the spectrum of agents causative of pneumonia is similar to that affecting the general population. Pneumonia increases the risk of preterm labor and fetal mortality. The clinical presentation of pneumonia in pregnant patients is similar to that of the general population, although pregnancy limits antibiotic treatment choices due to teratogenic effects on the fetus. Food and Drug Administration (FDA) classifications in pregnancy should be reviewed before drugs are prescribed.

Influenza is a cause of pneumonia in pregnant patients. Influenza antivirals are considered by many experts to be safe in pregnancy (despite being FDA category C) and should be used without delay in pregnant patients presenting with symptoms concerning for influenza. Coexisting bacterial infection in pregnant patients can complicate severe influenza pneumonia; empirical antibiotics are recommended in critically ill patients. Pregnant patients with primary infection with varicella zoster virus are at increased risk of pneumonia and death.

Pregnant patients with HIV are at risk for preterm labor and pneumonia, most commonly *Pneumocystis* pneumonia (PCP). Because HIV screening is ubiquitous in pregnant patients, most adherent patients with HIV are already receiving appropriate antiretroviral and prophylaxis regimens as indicated. PCP leads to respiratory failure requiring mechanical ventilation in approximately 60% of patients. Despite being FDA category C, trimethoprim-sulfamethoxazole is recommended in pregnant patients with PCP because of the high mortality rate. Recommendations for the use of corticosteroids in patients with PCP are unchanged in pregnancy.

Amniotic Fluid Embolism

The exact incidence of AFE is unknown, but it is believed to occur in approximately 1 in 10,000 to 50,000 births. Despite its low incidence, AFE accounts for approximately 7% of all maternal deaths. Approximately half of AFE cases occur before or at delivery, while half are postpartum. The signs and symptoms of AFE include hypotension, dyspnea, coagulopathy, and hemorrhage. Acutely ill patients typically have right ventricular shock followed by subsequent vasodilatory shock. It has been suggested that AFE be renamed "anaphylactoid syndrome of pregnancy."

When AFE occurs prior to delivery, the most immediate consideration should be delivery of the fetus. This is associated with the best fetal outcomes and simplifies resuscitation of the mother. Because AFE is almost invariably associated with hypoxia, tracheal intubation and mechanical ventilation with 100% oxygen are indicated. In patients who develop severe acute hypoxic respiratory failure, lung-protective ventilation with high positive end-expiratory pressure might be required. An arterial line should be inserted for blood pressure monitoring and blood gas analysis. Central venous access should be established to facilitate the infusion of fluids and vasoactive agents if the clinical situation requires. Echocardiography is crucial in resuscitation and the selection of vasoactive agents, since shock can be multifactorial and dynamic. Significant hemorrhage and DIC complicate most cases of AFE, and volume resuscitation with blood products is often required.

Venous Air Embolism

Venous air embolism may account for 1% of all maternal deaths. It can occur during normal delivery, delivery with placenta previa, abortion, and cesarean section. Symptoms in the awake patient include sudden cough, dyspnea, dizziness, tachypnea, tachycardia, and diaphoresis. In the anesthetized patient, an abrupt decline in the end-tidal carbon dioxide, often accompanied by hypotension, desaturation, or an abnormal heart rhythm, is highly suggestive of air embolism. Sudden hypotension is often followed by cardiac arrest. The cardiac examination may reveal a "mill-wheel" murmur over the precordium. The electrocardiogram may demonstrate right-sided heart strain, ischemic changes, or a variety of arrhythmias. Survivors of the acute event are likely to develop a short but severe course of ARDS.

When the diagnosis of venous air embolism is suspected, the patient should be

supported with 100% oxygen and the infusion of volume. If embolism occurs during a surgical procedure, surgeons should be requested to flood the portion of the surgical field where venous sinuses might be present. Echocardiography should be used to evaluate the patient; air emboli are often visible in the right atrium, right ventricle, and pulmonary arteries. Left lateral decubitus and Trendelenburg positioning may be helpful. Therapy with hyperbaric oxygen is generally not feasible for an unstable patient. Most current guidelines recommend that patients who have air embolism be managed with infusions of norepinephrine and dobutamine to support right-sided heart function in the face of the increased afterload associated with air-obstructed pulmonary arteries.

Thromboembolic Disease

PE accounts for 10% of maternal mortality. The risk of thromboembolic disease is increased substantially in pregnant patients, lasting throughout pregnancy and postpartum. Thrombophilia and a history of deep vein thrombosis (DVT) are significant risk factors for DVT during pregnancy. Smoking at any time during pregnancy, cesarean delivery, obesity, and preeclampsia are also risk factors. Isolated iliofemoral DVT occurs most commonly in pregnant patients, and thus the risk of associated PE is likely higher in pregnant women than for the general population.

The diagnosis of thromboembolic disease in pregnant patients is complicated by the presence of subjective dyspnea and dependent edema in normal pregnancy. Pregnant patients with PE can present with abdominal pain, leukocytosis, and fever in addition to the typical symptoms of chest pain and dyspnea. Although the D-dimer level can be elevated during normal pregnancy, a negative value in conjunction with a negative compressive ultrasound test is useful to rule out DVT. When available, compression ultrasound is the initial diagnostic test of choice for DVT in pregnant patients and may be performed prior to evaluation for PE, because a positive study or a high index of suspicion (even prior to diagnostic studies) is sufficient to initiate anticoagulation. Ventilation-perfusion scanning and PE-protocolled CT imaging are diagnostic studies for PE. Thrombolytics may be indicated when shock is present.

Warfarin crosses the placenta and is contraindicated (FDA category X) in pregnancy. Heparin (category C) and low-molecular-weight heparin (category B) do not cross the placenta and are the mainstays of treatment for DVT and PE in pregnancy. Renal function in pregnancy may alter excretion of heparin and low-molecular-weight heparin, making the pharmacokinetics unpredictable.

Fondaparinux should be considered in patients with a history of heparin-induced thrombocytopenia. In rare instances where anticoagulation is absolutely or relatively contraindicated, an inferior vena cava filter can be positioned suprarenally.

Asthma

Asthma complicates 4% to 8% of pregnancies in the United States. Asthmatic patients are believed to be at greater risk for preterm labor, pregnancy-induced hypertension, preeclampsia, and chorioamnionitis. Management of asthma in the pregnant patient is similar to that of the nonpregnant patient. The most important difference is that an arterial P_{CO_2} greater than 35 mm Hg indicates respiratory failure. Inhaled β-agonists and steroids are used in the same manner as in nonpregnant patients. The use of heliox in conjunction with noninvasive positive pressure ventilation (NIPPV) can avert intubation and mechanical ventilation.

Mechanical Ventilation

The escalation of support for the pregnant patient with respiratory failure varies among institutions. NIPPV is often the first step in the support of non-ARDS respiratory failure. NIPPV failure is marked by (1) arterial P_{CO_2} continuing to increase after 60 minutes of NIPPV, (2) persistent hypoxia, (3) concern for respiratory fatigue with a persistently elevated respiratory rate (typically >40 breaths per minute), or (4) mental status deterioration. Pregnant patients often have engorged nasal and oropharyngeal mucosa, which produces both a decrease in airway diameter and an increased risk of bleeding with instrumentation. These anatomic changes, in combination with incomplete gastric emptying, increase the risks associated with intubation for pregnant patients.

The use of mechanical ventilation in pregnancy entails several important considerations. Sedation with the combination of fentanyl or morphine (both FDA category C) and propofol (category B) is considered safe. If paralysis is required, cisatracurium (category B) is a preferred agent. Eucapnia in the pregnant patient is defined by an arterial P_{CO_2} of 27 to 32 mm Hg, which is likely optimal for uteroplacental vascular autoregulation. The goal levels of oxygenation in the pregnant patient are a P_{O_2} of 70 mm Hg and oxygen saturation greater than 95. The least amount of positive end-expiratory pressure required to obtain these goals using a nontoxic fraction of inspired oxygen (F_{IO_2} <0.6) is recommended. Peak airway and plateau pressures in pregnant patients

are generally higher than in nonpregnant patients for a given degree of pulmonary disease due to the gravid uterus. Tidal volumes of 5 to 6 mL/kg should be targeted. Elevated plateau pressures may be necessary to avoid significant hypercapnia. The patient should be positioned as close to left lateral decubitus as possible to facilitate uteroplacental perfusion.

OTHER DISORDERS OF PREGNANCY

Acute Renal Failure

Acute renal failure in pregnancy is associated with preeclampsia, sepsis, HELLP syndrome, or acute fatty liver of pregnancy. Renal failure associated with preeclampsia or the HELLP syndrome typically resolves with delivery of the fetus. Acute tubular necrosis may be caused by sepsis or hemorrhage. Acute cortical necrosis is associated with placental abruption, septic abortion, prolonged intrauterine retention of a dead fetus, hemorrhage, and AFE. In some patients, cortical necrosis progresses to end-stage renal failure requiring hemodialysis. Idiopathic postpartum acute renal failure is rare (it may be a variant of preeclampsia without hemolysis or thrombocytopenia) and occurs days to weeks after an otherwise unremarkable pregnancy and delivery. Corticosteroid therapy or plasmapheresis often is associated with clinical improvement or resolution.

Acute Liver Failure

Acute liver failure is an uncommon complication of pregnancy. Serum alkaline phosphatase increases during the first 7 months of pregnancy and peaks at 2 to 4 times normal near term. Serum albumin decreases during pregnancy. Other alterations in liver function are uncommon.

Subcapsular bleeding and hematoma formation are among the complications of preeclampsia and the HELLP syndrome. Acute fatty liver of pregnancy occurs in approximately 1 in 10,000 pregnancies and leads to liver failure, coma, and renal failure. The syndrome, which rarely presents before the 26th week, peaks at the 36th week and has been reported to occur in postpartum patients. The cause is unknown, but microvesicular infiltration of the liver is the common pathological finding. Risk factors include male fetus, primipara, and multiple gestations. Patients may present with headache, nausea, vomiting, right upper quadrant pain, malaise, and anorexia. Hypertension, peripheral edema, and proteinuria may be

present. Jaundice from cholestasis evolves subsequently, typically over the next several weeks. Right upper quadrant ultrasonography excludes gall bladder disease and often demonstrates increased echogenicity in the liver. Abdominal CT may demonstrate decreased attenuation from the fatty infiltrate. Liver biopsy is often accomplished via the transjugular approach to minimize the risk of bleeding in the already coagulopathic patient. In addition to entailing liver failure, coma, and renal failure, the clinical course is often complicated by pancreatitis, hemorrhage, seizures, and DIC. Delivery of the fetus is the definitive treatment for the syndrome. Maternal and fetal mortalities are believed to be less than 20%.

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CHAPTER 48

A Perspective on ICU Administration

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Key words: ICU administration, ICU management, ICU operations

No two critical care units are alike. While there are commonalities—patients, families, nurses, physicians—differences abound. Tasks are allocated differently among physician trainees, nurse practitioners, and/or physician assistants. Physicians' expectations and actions are different in "open" versus "closed" units. Patient populations can be separated according to medical discipline or can be mixed. These and other variations impact unit performance in the domains of quality, value, and access.

This chapter is intended for ICU leadership. The purpose of the chapter is to offer a process for creating a management construct that is robust to changing needs, transparent and responsive to stakeholders, applicable to a wide range of ICUs, and scalable from critical access hospitals to entire healthcare organizations. To a great extent, this chapter represents the opinions of the authors. *Caveat lector.*

MISSION VERSUS ATTRIBUTES: PRIORITIZING THE STAKEHOLDER PERSPECTIVES

The mission of a particular critical care unit is commonly identified in its name: medical ICU, coronary care unit, burn unit, and so on. That name defines the largest group of patients who are served by that unit. The attributes of the unit are typically less well defined. By *attributes*, we mean the properties of the care that are important to the stakeholders and therefore define the dimensions by which stakeholders will evaluate performance of the unit. Attributes may include access, value, focus, flexibility, research support, teaching, fairness (in the sense

of social and distributive justice), patient-family centeredness, quality, satisfaction, communication, and enabling of other hospital services.

The first step in ICU administration is to gather a complete list of attributes that the stakeholders deem potentially important to the critical care unit. Then, aggregate similar attributes (eg, cost-sensitive, cost-conscious, affordable) into a single attribute such as cost.

The second—and perhaps most important—step in ICU administration is to force the stakeholders to prioritize those attributes. A simple way to do this is to prepare 1 or more decks of index cards inscribed with 1 attribute per card and then ask each stakeholder to order the cards from most to least important. Emphasize that none of the attributes is unimportant, but some inevitably must take precedence over others. Such a forced ranking demands that each stakeholder consider the universe of attributes offered by the entire stakeholder community. In the event that there is not early consensus, the bottom half can be discarded and another round of rankings performed.

Regardless of the method selected, reaching not only consensus but also clarity around the meaning of those attributes is foundational to success: "If you don't know where you're going, any road will get you there."

When this exercise was performed at a large academic health science center including stakeholders in the broad range of critical care units, 3 attributes rose above all others:

1. Quality, by whatever measures were chosen by the ICUs themselves
2. Value, such that high-quality care was delivered at a cost that was affordable by patients, payers, and the healthcare system
3. Access, so that every patient who needed and could benefit from critical care would be offered critical care promptly

It is important to identify and prioritize attributes locally. One set will not fit all. Stakeholder engagement and transparency of the process are key, because the attributes that emerge as most important shape principal goals of that unit. The distinction between attribute and goal is subtle and merits reflection. Attributes are woven through people and the processes that make up the daily work. Goals are well-defined targets that, when achieved, enhance the core attributes. To illustrate, "reduce emergency department boarding hours by 50%" is a goal that

speaks directly to timely access to the ICU. However, goals may serve more than one key attribute: Thus, reducing emergency department boarding time may also increase the quality of care delivered to critically ill patients as well as to patients who would otherwise have to wait for emergency department care.

FROM GOALS TO CORE STRATEGY

Goals inform strategy. Further, any particular goal can be achieved through a variety of strategies (eg, cost reductions could be achieved by modifying labor force, reducing pharmacy expenses, and reducing complications and associated extended stays).

Achieving several goals simultaneously can be difficult. For example, if quality, teaching, and cost management were chosen as key attributes, quality and teaching can run counter to cost control as there are expenses associated with having learners in the environment: Novices make errors that erode quality. Yet both quality and teaching can be enhanced through scenarios and simulations that develop competencies and promote consistency. It would make sense in a unit focused on those attributes to devote resources to protected teaching time, linkage with a simulation center, team training, and similar activities. A strategy that focused the unit on becoming a regional or national leader in simulation-based training would enhance the attributes and also suggests a business plan for recouping the learner costs by offering the training to a wider audience.

Selecting the core strategy is the third essential step in ICU administration. ICU leaders must invest time in discovery and consideration of alternative strategies. Advice should be widely sought, but unlike the selection of key attributes, selection of the core strategy is a responsibility that rests solely with the ICU leadership team. The ICU leadership team will be held responsible for execution. The core strategy must therefore be workable and it must achieve those attributes that have emerged as the foci for the unit or the larger healthcare system. Discovering a strategy that achieves several goals and advances multiple attributes simultaneously requires ingenuity. Pursuing that strategy will require both patience and tenacity.

When our group considered the attribute triplet of quality, value, and access, the core strategy that emerged was transformation of our critical care from a low-reliability to a high-reliability model. By *low reliability*, we mean an emphasis on the uniqueness of every patient and a passion for finding a perfect solution to each particular situation. By *high reliability*, we mean the development of highly

consistent practices that produce predictable results. A high-reliability model should improve quality because we will recognize unexpected consequences sooner and correct adverse events earlier. It should improve value because it will reduce variability as we use fewer alternatives more effectively. It should improve access because standard approaches can be more efficiently disseminated and applied.

Failure to explicitly link a core strategy to the attributes driving the unit's goals is a recipe for failure of the management team. The initial strategy may prove unworkable, ineffective or incomplete. However, failure to define and embrace the core strategy guarantees diffusion of effort that will lead to mediocrity at best and potentially to collapse of the unit.

EXECUTION: MORE THAN STRATEGY

Strategy must be executed, but strategy by itself cannot be executed without 2 additional components: people and an operational plan.[1] In the ICU, the twin questions are (1) is the right workforce present and (2) are the specific workers assigned the right tasks at the right time with the right knowledge, training, and equipment and assorted into workgroups that will get the job done right. A familiar example (in microcosm) is execution of central line insertion. The typical strategy is to follow best practices including use of ultrasound guidance, full barrier precautions, patient positioning, and so on. The workforce typically includes a qualified operator, a qualified colleague to pass materials, and a qualified nurse to prepare the IV line, calibrate the monitors, make the connections, and apply the final dressing. The operational plan is often defined and supported by a checklist that promotes and documents completion of essential steps including the follow-up radiograph for verification of line location.

WORKFORCE

Workforce has to match strategy. This matching may require training, hiring, reallocating, repurposing, and even dismissing current workers. For example, if development and use of simulations emerge as a core strategy, it is self-evident that someone must have the skills to develop the strategy and serve as facilitator when learners are learning in the simulator. Those skills are neither common nor heritable. They must be acquired either through hiring new personnel or retraining and repurposing current personnel.

The general structure of the workforce in critical care units suggests that there are 3 classes of workers: constant workers, cyclic workers, and temporary workers. The constant workers include the nursing staff and any dedicated respiratory therapists, pharmacists, nutrition support staff, and others who have no other professional responsibilities outside the ICU. They serve as the collective memory of the unit, know and execute procedures with the greatest consistency, and provide the glue that holds the other classes of workers together. The cyclic workers include the attending intensivist staff. This is often a team of half a dozen physicians who are dedicated to the ICU part of the time but also have professional responsibilities elsewhere outside of their ICU tours of duty. Other cyclic workers can include physical therapists, respiratory therapists, and pharmacists who have duties elsewhere in the medical center. The temporary workers are most often trainees who come to the ICU as part of scheduled rotations. Although they are officially learners, many if not most ICUs that host trainees are exchanging training for service (meaning that trainees provide direct care to patients under varying levels of supervision).

Workforce challenges are increasing in the United States. These challenges are manifest in several ways, including image and burnout.[2,3]

Professional competencies in critical care units are asserted through licensure, board certification, and staff privileging. Although nurses and allied health personnel often must complete "skills days," during which they demonstrate specific competencies to a specialty educator, planned verification of physician competencies is less common. Physician trainees can be especially heterogeneous with respect to competencies and are not infrequently called upon to perform complex and even invasive tasks after limited training and experience.

The fourth step in ICU administration is, therefore, to assess the scope, depth, and competencies of the workforce that will be tasked with executing the strategy. When we considered our core strategy of transforming critical care from a low-reliability to a high-reliability activity, it became apparent that we needed another class of workers who were committed to standardization, were willing to undergo regular verification of their competencies, and could become constants in the workforce. We created teams of critical care affiliate providers, including both acute care nurse practitioners and physician assistants who are dedicated to their assigned ICUs.

COMMUNICATION IN CRITICAL CARE

Substantial evidence points to the importance of communication in critical care and to the failure of ICUs to develop and sustain excellent communications among their workforce, patients, and families. From an administrative standpoint, the single most important resolution that can be made by ICU leadership and projected throughout the ICU is to set perfect communication as a standard and not a goal. Perfection in communication cannot be approached without structure, without a willingness to expose and resolve ambiguity, and without a commitment to examine communication failures and their contribution to adverse outcomes.

The greatest barriers to perfect communication are anxieties over conflict. The anxieties are real, as are the conflicts. Both can be resolved professionally and collegially. What cannot be resolved are the errors attributable to miscommunication. Three elements form a foundation for perfect communication:

- *Create a durable and generalizable communications framework.* A convenient strategy is to focus on systems within patients (including physiological and sociological systems). Within each system, use a consistent, 4-element structure to discuss (1) the current state of the patient, (2) the treatments driving the current state, (3) the desired state or goal, and (4) what will be changed or done to move from the current state to the desired state. A moment's reflection will lead one to conclude that this is a formal implementation of SBAR (situation, background, assessment, recommendations).[4] Finally, a summary of decisions resulting from those system-by-system communications (the order read-back) will go far in ensuring that the entire team has digested the substance and implication of the discussions.

- *Invest time in reaching consensus on standard approaches.* What circumstances justify transfusion? Given hemodynamically normal atrial fibrillation with rapid ventricular response, does this unit use amiodarone, diltiazem, or a β-adrenergic blocker as the first step? What criteria justify discontinuing empirical antibiotic therapy? These are 3 among many common situations in the ICU. The usual answer is that it depends. Investing time to establish the standard approach catalyzes essential communication when a team member decides that a particular patient's condition justifies an exception to the standard.

- *Empower and expect every member of the care team, including the patient and family, to call for clarification in the face of uncertainty.* With some frequency, clarity cannot be immediately achieved because some data are missing or the outcomes of other actions must be assessed. Acknowledging those situations is of obvious significance. Of even greater significance, however, is reconciliation of opposing positions. With fair frequency, different team members see situations differently. The patient is either too dry or too wet, too sedated or not sedated enough, and so on. Lack of clarity will lead to opposing treatments: fluids and diuretics, stopping one opiate while starting another, and so on. Such circumstances simply must not be permitted.

There is often a fear that exposure of ambiguity and even conflicting opinions will lead to embarrassment, hurt feelings, and loss of confidence. It is up to the leadership team to ensure that professionalism is maintained and that requests for clarification are always received in a safe haven. It is essential not to burden nurses and allied health personnel with the task of resolving conflicts between physicians.

OPERATING PLAN

Simply assembling a workforce and announcing the core strategy will lead to general confusion. By analogy, fielding great football players and simply announcing that the most likely winning strategy against the opposing team will be a passing game will almost certainly result in defeat. The team has to develop, practice, and play according to a game plan that maps who is supposed to do what, how, and when. The game plan is not the playbook. The game plan sequences and integrates plays from the playbook.

In the ICU, the operating plan has to exist at a higher level than a standard operating procedure that guides (for example) insertion of a central line. In the ICU, the operating plan has to exist at a lower level than the metric goals. ("Reduce ventilator-acquired pneumonia by 25% annually" is a goal, not an operating plan.)

The operating plan in the ICU determines how personnel are allocated, how they will interact with one another, how they will come together to promote best practices, and how they will collectively assess their performance. The operating plan has to marry the workforce with the core strategy so that the obstacles to the attributes can be surmounted or circumnavigated. In short, the operating plan

describes how things are going to get done.

More comments about the design and implementation of the operating plan follow later in this chapter, after the discussion of resources and investments. For now, it is enough to remember that there are 2 general obstacles to achieving any particular goal in the ICU that every operating plan must confront.

First, the rhythms of ICU activities synchronize rarely and, then, often poorly. Nursing care is continuous, with best practice often dictating a summary and update as frequently as every 4 hours. Two rounds with attendings traditionally occur once daily, with perhaps a planned mini-round in the evening. The pharmacy decides that total parenteral nutrition is delivered daily at 8 pm. Physical therapy is available Monday, Wednesday, and Friday. And so on. The operating plan needs to address such asynchronies.

Second, tasks in the ICU tend to group along professional lines such that communication across professions is insufficient to promote situation awareness. For example, a respiratory therapist adjusts the ventilator, a nurse obtains the arterial blood gas reading from an indwelling catheter, a physician interprets the data, and a radiologist looks at the chest radiograph. It is therefore unsurprising to learn that increasing airway pressures (known to the respiratory therapist), decreasing arterial pressures (known to the nurse), and progressive hypoxemia (known to the physician) can coexist for hours before a radiologist alerts the team that the patient has a sizeable pneumothorax. Poor situation awareness in the ICU is unfortunately common and commonly morbid. The operating plan needs to enhance situation awareness so that all team members can improve their effectiveness. The fifth step in ICU administration, then, will be to compose an operational plan that interdigitates with the workforce and the core strategy.

RESOURCES AND INVESTMENTS

Critical care units are high-cost, high-risk patient care areas that combine human and technical assets to reverse threats to life, stabilize physiological status, and liberate patients from mechanical and drug supports. Financial costs are high and the costs of mistakes are higher still. Thus, every administrative plan must be explicit about what resources are required and what investments should be made in acquiring, maintaining, updating, and eventually replacing space, technology, and personnel.

One way to inform decisions about new investments is to relentlessly ask 2

questions: What resources are currently available? What additional resources are necessary to advance the core strategy? The key words in the questions are *available* and *necessary*.

Although human resources are often both overtaxed and in short supply, devices and facilities may be more plentiful. Different from other areas of the medical center (and from umbrella organizations such as universities), ICUs and their personnel have 24×7 work schedules. This distinction can present opportunities. For example, personnel from the local simulation facility may well plead that it is totally booked until they learn that you and your staff are available for training evenings and on weekends, when other users might not be willing to train.

The sixth step in ICU administration is to clarify what resources are available to address local core strategies. The harder questions involve resources that are necessary but unavailable. If, for example, a core strategy involves continuous education but there is no qualified educator on staff, one must be hired. (It is the rare clinical physician who has the time and possesses sufficient training and experience to fulfill the educator role.) Technical resources may need to be evaluated and purchased or designed and created. If, for example, a core strategy is to perfect communication, then it may be necessary to upgrade or modify electronic charting and displays.

Inevitably, someone will assert a particular resource to be necessary—a new monitor, a new ventilator, a new device, a new position, or a new role. Two sets of questions can guide the response. First, what data are available to quantify the benefit to patients and the ICU of the new personnel or technology? What have others experienced, and is that experience relevant? What is the clinical argument? Second, how will the cost be managed? How will acquisition of the resource improve the value of the care that is provided, understanding that value relates quality to cost? What is the business case for the new investment? Strategic investment of limited resources requires a thorough analysis of the clinical case and the business case. The seventh step in ICU administration is to identify the source of investments.

Perhaps the most commonly voiced complaints from ICU leadership teams are that the hospital or medical center either has no money to invest in the ICU, has repeatedly refused to invest during the annual capital expenditure event, or has listened to someone else whose priorities do not address the needs of the ICU. There are 2 common reasons for failure to secure the investment. First, there is something amiss with the pairing of the business case and the clinical case. The

director of business operations supervising the ICU should be intimately involved with creating the business case for the investment. Second, the business and clinical cases are poorly aligned with larger efforts of the hospital or health science center. A case that does not align with the organization's priorities is unlikely to be funded. If the ICU's core strategies significantly differ from the organization's strategic plan, one may need to reassess the reasons for the divergence.

Certain investment justifications are made more easily than others. Examples include these:

- A regulatory agency dictates a specification that must be met to continue ICU operations.
- A new service line bundle includes an activity that occurs in the ICU.
- Recruitment of a new physician or group to the hospital or medical center incurs special critical care needs.

What binds these examples together is that each describes a response to influences external to the ICU. It is essential that the ICU leadership team continuously assess its role and contributions to the hospital and medical center as they exist today and as they are likely to change tomorrow. Acquiring new franchises (eg, becoming first responders to "codes," assuming responsibility for hospital-wide telemetry, and supervising elective placement of central lines) is a time-honored approach to garnering additional human and physical resources. To paraphrase the late President Kennedy, ICU leaders should ask not what their medical center can do for their ICU but rather what their ICU can do for their medical center.

The sources of money are specific to individual medical centers. Again, the director of business operations should be fully conversant with all of these sources. Typically there is an operating budget; capital expenditures over the operating budget; grants and contracts; and sometimes targeted philanthropy. It is often overlooked that access to each of these requires prior demonstration that the leadership team can effectively steward resources.

RESOURCE STEWARDSHIP AND THE OTHER CVP

The ICU leadership team must have a shared working knowledge of ICU financing. What commonly happens is that the ICU nursing director has access

to and control over personnel and supplies and knows his or her budgets cold. The ICU medical director has information about treatment utilization but often has little information as to which physicians are ordering what treatments and even less information as to how those treatment decisions affect the bottom line of the hospital. The director of business operations knows the consequences of staffing, supplies, and physician decision making but lacks the clinical background to know how to initiate (much less sustain) changes that will augment value to the ICU and to the hospital as a whole.

It should be apparent that the 3 leaders must educate each other in order to communicate effectively and that communication is key to developing a comprehensive plan for ICU stewardship. Learning to read a spreadsheet together and understanding how funds flow among the hospital, the physician organization, and the medical center are important first steps. Some frustration early in the process is inevitable as the peculiarities of local accounting and cost-volume-profit analyses become evident.[5] Put simply, the cost-volume-profit relationship ("CVP") is as important to the unit as the central venous pressure is to the patient. The frustrations are more than offset by discoveries of the magnitude of certain expenses and how modest changes in behavior can lead to enormous cost savings. Specific areas worthy of scrutiny begin with anything that is scheduled daily—laboratory tests, imaging, electrocardiographs. Next, an examination of practice versus evidence-supported guidelines (eg, transfusion of red blood cells) will often expose opportunities to improve care while reducing costs.

The eighth step in ICU administration involves developing a common framework and language around resource stewardship.

THE UNIT MEETINGS

Names of the meetings change from one hospital to the next, but every successful ICU organizes regularly scheduled meetings in which all team members (typically through selected representatives) convene to discuss ICU performance. The topics—and sometimes the meetings themselves—typically are divided into 3 components: past, present, and future.

Review of past performance typically includes review of unexpected morbidity and mortality, follow-up of challenging patients discharged to the floor or long-term care, and similar outlier analysis. The patients can often be presented by novices as a learning strategy followed by discussion among senior personnel.

These should be labeled as *peer-review meetings* and benefit from protection from medicolegal discovery. The convener should rigidly enforce 2 rules: First, the meeting is a safe haven such that all perspectives are aired without prejudice, and second, the meeting is conducted with as much rigor and objectivity as possible. This meeting is often called the *M and M meeting*.

Present activities typically focus on quality metrics and their trajectories, evaluation of the current month's learners, adherence to and performance of key protocols and procedures, enrollment in ongoing research studies, and semiblinded reporting of individual physician performance. It can be especially helpful to invite quality-focused personnel including the epidemiologist, the infection control officer, the risk manager, the study coordinator, and the business director to present segments of this component using standard tools. This meeting is often called the *quality meeting*.

As experience and efficiency are gained in discussing past and present, the focus of the meetings will shift toward creating a better future. Here, a structured discussion of priorities and plans should engage the entire group. Reference to the key attributes and the core strategy is not only useful but necessary. It is in this segment that opportunities for aligning unit goals with larger initiatives are best entertained. What professional meetings are coming up that might be appropriate for abstracts? Are there national initiatives such as the Surviving Sepsis Campaign, National Critical Care Awareness and Recognition Month, or perhaps a regional meeting of a professional society that could be leveraged to advance one or more of the attributes? This meeting is often called the *strategy meeting*.

Regardless of the divisions or consolidation of the topics and the meetings, engagement of the entire ICU community is important to success. Care should be taken to avoid disenfranchising night and weekend staff because they work unsocial hours.

ADMINISTRATIVE MODELS

This chapter has been silent on administrative models: closed, semiclosed, open. The reason for the silence is that these traditional divisions serve caregivers more than they serve patients and families. The closed model assigns all responsibilities to the ICU team: The on-site ICU doctor becomes the attending physician of record, whereas the physician and team who sent the patient to the ICU in the first place are relegated to "interested observer" roles. The open

model is the mirror image: Typically there are no intensivists, and the admitting physician retains all authorities and responsibilities even though she may be physically present for only a few minutes each day. The semiclosed model attempts to allocate specific responsibilities to the admitting team and the balance of responsibilities to the ICU team and often leaves both teams either uncertain or in conflict over the most appropriate next steps.

The more appropriate focus is on the patient and family, where the best outcomes will emerge from collaborative comanagement of the patient. This is no different than the collaborative approach in the operating room, where the surgeon is focused on a specific procedure while the anesthesia provider addresses analgesia, anesthesia, and comprehensive multisystem support. Safe, efficient, and effective care is promoted by an appropriate division of labor, adherence to protocols, and clarity in communication among the caregivers.

The preponderance of evidence supports care coordination, typically by an intensive care physician who is responsible for recognizing and reconciling discrepancies in care proposed not only by the admitting and the ICU teams but also by specialty consultants who are called in on the case.[6] Once again, communication is a prerequisite to coordination. The prevailing Leapfrog standard requires engagement and availability of an intensivist to all patients admitted to the ICU.

This chapter has been equally silent on critical care organizations (CCOs). The importance of a coordinated organization in the achievement of unit-specific and institutional goals cannot be overstated. A detailed review of critical care organizational models has been presented.[7]

CONSISTENCY EMERGES FROM TEAM TRAINING

Consider the common situation in which an ICU patient must be emergently intubated. A typical 16-bed ICU employs about 50 nurses, is staffed by 6 attending physicians, and is served by 4 respiratory therapists. If the intubation team consists of a nurse, a physician, and a respiratory therapist, there are 1,200 different combinations that might constitute the intubation team. Yet emergent intubations are performed as lifesaving procedures, and therefore each just-in-time team must perform flawlessly. The only way to achieve the desired, consistently excellent performance is to have each team member train to a common standard.

Team training typically begins with structured short courses such as Advanced Cardiac Life Support and Fundamental Critical Care Support. The leadership team is responsible for determining who should take such courses and how the costs of training are to be managed. Such courses are focused on having individuals perform similarly in common situations.

The second level of team training typically is scenario based and uses increasingly realistic simulators, progressing from simple computer displays to animated mannequins and then to large animals. These simulations may include timely recognition of impending catastrophes and performance of specific procedures. The most important aspect of scenarios and simulators is to let team members practice coordinating their actions under progressively difficult circumstances. Different from coursework, where learning is demonstrated through success on written or practical examinations, scenarios and simulations are most effective when the team fails, dissects the cause of the failure, evaluates alternatives, and then reruns the simulation to a successful conclusion. Optimal team training in the simulator includes *Kobayashi Maru* scenarios that result in an adverse outcome no matter how efficient the response to the catastrophe.[8]

The third level of team training is exploratory and is used to make strategic decisions among physical, technological, and social innovations as they become available. Team training on new hardware and software in actual or virtual environments confronting complex unit-wide situations (eg, simultaneous codes or a widespread electrical failure) will provide insight into the team's responses to novelty while informing difficult and expensive decisions.

It is evident that team training is costly. It should be equally evident that failure to fund and pursue team training is costlier still. Enterprises that take on substantial risk—the military, airlines, power companies, to name a few—consistently invest in training to mitigate those risks. Critical care cannot afford to omit team training.

TEAM GOALS

Building a cohesive critical care team takes "blood, sweat, and tears." Creating team goals will promote team building. In order for these goals to be effective, every provider in a unit must work toward the same goal and target.

In the United States, ICU providers are familiar with quality metrics that aim to reduce hospital-acquired infections and so-called "never events." Many

physicians are also familiar with incentive compensation based on relative value units (RVUs). RVU incentives are typically set at the individual provider level. This yields competition among providers and erodes teamwork. RVUs are also problematic from a critical care billing standpoint in the United States. Adult critical care billing is based on time in minutes provided to each patient. Therefore, it is possible to have multiple critical care bills or codes per patient. This is different from the outpatient setting, where each patient can be billed only one code for the visit—excluding procedures.

Incentives that directly impact quality, value, and access have been successful in various studies.[9-12] Metrics can target overuse of resources (eg, laboratory tests, radiographs, blood products, antibiotics, colloids), increase the amount of time providers spend with patients and families, improve time to treatments and therapies (eg, early goal-directed therapy for septic patients, palliative care involvement, nutrition implementation), or effect process improvements (eg, ultrasound-guided central line insertions, bundle compliance, progressive mobility, standard ventilation weaning protocols).

Numerous incentive metrics can be selected, but providers must have input into both the selection of metrics and how they will be measured. The metrics and targets must be readily understood by providers to ensure they can develop an effective improvement plan. The targets must be realistic. Using baseline data on each unit to set targets is the best way to ensure attainability. A monthly report should be sent to all providers—a lack of feedback will ensure failure and discourage future engagement. Leaders must provide drilldown data (ie, patient-level data) to units that are not improving and hold meetings to share best practices among units.

A successful incentive plan can increase collaboration both within the unit and between units and can build relationships. A poorly executed plan can create rifts among team members and weaken morale.

EXECUTION

We have already observed that execution requires strategy, a workforce, and an operational plan. But how, precisely, do a group of talented individuals, once they are appropriately trained and equipped with a series of standard approaches, come together to achieve goals for patients and families? Although experienced team members readily identify characteristics that lead to success—effective communication, learning from mistakes, and so on—few can describe a process

that leads to consistently effective execution.

The discrepancy between knowing what is needed to achieve success and the achievement of success is rooted in tradition, namely the traditional Deming (or Shewhart) process improvement cycle of PDSA—plan, do, study, act. Although process improvement is surely important to quality, it is different from execution toward objectives.[13,14]

If there are objectives to be achieved, and daily care of the critically ill patient and of the unit involves achieving objectives, then planning has to make the objective clear, identify the resources and the threats, bring standard procedures and experience to the table, develop a course of action, and consider "what-if" contingencies.

Planning is followed by briefing. In simplest form, the briefing summarizes the plan and assigns specific tasks to owners. The briefing frames the scenario—what makes this patient or this situation unique. It unambiguously restates the objective. It prioritizes the resources and addresses the most likely obstacles. It assigns tasks to people. It makes sure there are planned responses to adverse outcomes.

Execution is goal specific, but there are general tools that contribute to success, such as checklists, scripts, and flows. Real-time redistribution of tasks (sometimes called *task shedding*) is often crucial in the ICU.

Once execution is complete, some form of debriefing is necessary to identify what went well and what can be done differently next time. This will transfer experience to the next planning phase. Generally, debriefs should be prompt, objective (without accusation), and analytical (getting to the root cause), yielding lessons learned.[15]

A BRIEF NOTE ON POPULATION MANAGEMENT AND TELE-ICU SERVICES

To the extent that standardizing care becomes a core strategy toward improving the high-priority attributes, the ICU must create additional lenses through which to view populations. These populations may include the current census of the ICU, cohorts of patients linked by particular admission criteria, or patients who had a common complication or some other defining characteristics. Dashboard-like displays that both measure performance and prompt an immediate intervention (such as a green-red light display showing which patients are

receiving drug prophylaxis against gastrointestinal bleeding), although surely useful as memory joggers, are by themselves insufficient because they do not link action with outcome. More simply, they confuse adherence to process with the achievement of goal. A larger population view might ask which antacid drugs are being given, what is the cost, whether utilization is rational, and what new evidence supports or questions their use as standard treatment.

The contribution of tele-ICU services to changes in morbidity, mortality, and cost of critical care is hotly debated.[16-20] What is not subject to debate is the fact that implementation of a tele-ICU changes processes of care, disseminates those changes across ICUs, and imposes a different structure on communications simply because those who are providing tele-ICU services are managing ICUs in multiple locations simultaneously. Population management is enhanced by standardization and dissemination of standards because it facilitates recognition of outliers—patients who do not fit standard protocols and patients who have unexpected responses to standard interventions.

SUMMARY

ICU administration is at once an art, a science, an activity, and a profession. This chapter touches on a few important tasks in ICU administration but cannot be considered comprehensive. After all, no comments were offered on the important subjects of coding and billing, compensation, the Affordable Care Act and new payment models, ICU design, role of palliative and hospice care, and ethics of administration including antibiotic stewardship and fair allocation during drug shortages. The list goes on.

The wonderful thing about ICU care and, by extension, ICU administration is that everyone understands it to be a team sport. Thoughtful administrators will look both inside and outside their unit for advice and guidance, including local resources (such as business schools and schools of public health) and national and international professional societies.

When asked for a single piece of advice for new ICU administrators, we often suggest that they pause before acting to ask themselves a question: Am I trying to manage a project, or am I trying to manage change? The tools and skill sets are different.

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CHAPTER 49

Severity of Illness Scoring Systems

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Key words: calibration, discrimination, outcome prediction, organ dysfunction

Severity of illness is a fairly nonspecific term referring to the seriousness or magnitude of a disease process and, by extension, the risk of complications and death; that is, the more severely ill a patient is, the more likely that patient is to succumb to the disease. Clearly, the ability to quantify severity of illness could be of use to clinicians and healthcare managers, and there has been considerable interest in developing techniques to measure severity of illness. We are all aware of individual patient characteristics that can affect mortality, such as age, certain comorbid diseases, serum lactate levels, and others. Severity of illness scores attempt to combine several such characteristics into more complex and complete scoring systems. Importantly, the term *severity of illness* will mean different things to different people, which will thus influence how it is measured and interpreted. For example, a general intensivist will be more interested in a global index in individual patients and how it may change in response to treatment; a nephrologist will be more interested in an organ-specific score assessing the severity of renal injury; a hospital manager will be more interested in how the severity of illness will affect resource use and costs; and a research team designing a clinical trial will be most interested in defining a homogeneous study population of patients or assessing the impact of an intervention on disease severity. Different scoring systems have thus been developed to meet these different needs. So-called generic scoring systems assess severity of illness in general ICU patients, whereas organ- or disease-specific scores have been developed for use in selected groups of patients or for specific situations, such as the Glasgow Coma Scale, Injury Severity Score, and Model for End-Stage Liver Disease. Scoring systems also have been created that link severity of illness to resource allocation, such as the Therapeutic Intervention Scoring System.

Since their introduction some 30 years ago, severity of illness scores have become a part of routine practice in many ICUs. Those most widely used in the general ICU environment, which is the focus of this chapter, can be broadly divided into 2 groups:

1. Outcome prediction scores that measure severity of illness once (at ICU admission) and use the score to calculate a risk of death, for example, the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Mortality Probability Model (MPM)
2. Organ dysfunction scores that can quantify the severity of organ dysfunction at admission and during the ICU stay, for example, the Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA)

OUTCOME PREDICTION SCORES

Three main outcome prediction scores are used in adult critical care medicine: APACHE, SAPS, and MPM. All were developed 30 to 35 years ago but have been altered and adapted over the years to make them easier to use or better suited to changing patient demographics. Similar scores have been developed for use in children, such as the Pediatric Index of Mortality. Importantly, none of these scores is designed for individual patient outcome prediction and should not be used as a basis for individual treatment decisions or as an entry criterion for clinical trials.

Once a prognostic system has been developed, it needs to be validated in populations other than that in which it was developed to determine how well it performs, that is, how accurate it is at predicting prognosis. To this end, 2 objective measures are widely used:

1. Calibration is a measure of how well the estimated probability of mortality compares with the actual, observed mortality across the whole spectrum of possible outcomes. Calibration usually is measured using the Hosmer-Lemeshow goodness-of-fit test and reported as the chi-square value: A score with good calibration will have a *P* value greater than 0.05.
2. Discrimination refers to how well the model predicts the correct outcome, that is, how well it discriminates between individuals who will live and those who will die. Discrimination is generally assessed by the area under

the receiver operating characteristic (ROC) curve.

As it is impossible for any model to have perfect calibration and perfect discrimination at the same time, a clinician who is selecting a score based on these 2 measures should consider the purpose for which the score is being used. For example, if the purpose is to compare quality of care between ICUs, better calibration is more important, whereas to predict outcome for individual patients, good discrimination is preferable.

A score's performance may vary from that reported in the developmental and initial validation studies for several reasons. First, data collection for score calculation needs to be performed in the same manner and following the same rules as were used during the development of the model in question. In addition, specific populations (eg, patients aged < 16 years, cardiac surgery patients, patients with burns, patients with a very short length of ICU stay) often were not included in the original development databases, and these scores may not be accurate if such patients are included in validation populations. Finally, changes in patient demographics, ICU admission policies, therapeutic measures, and the use of withdrawing and withholding decisions will influence the performance of outcome prediction scores.

Acute Physiology and Chronic Health Evaluation

The APACHE system was the first outcome prediction score to be developed and is the most widely used of these scores, particularly in the United States. Developed by Knaus et al in 1981 using a nominal group process, APACHE was designed as a "conceptual model of the key elements that influenced a patient's outcome from severe illness." In the original APACHE, the score was separated into 2 parts:

1. A score related to the health status of the patient prior to admission, including functional status, medical needs, and presence of chronic diseases over the 6 months prior to admission. Patients were allocated to 1 of 4 categories from A (previous good health) to D (severe restriction of activity because of disease).
2. A score related to the actual physiological status of the patient on admission. Thirty-four physiological variables were assessed over the first 32 hours of admission and awarded a weighted score so that sicker patients had higher scores.

A patient's APACHE classification, therefore, consisted of a number (the physiology score) and a letter (the chronic health status), for example, 33-B. Original and subsequent validation studies demonstrated that the APACHE score was consistently accurate in predicting ICU and hospital mortality rates in different hospitals and across different countries.

In 1985, Knaus and colleagues published the second version of APACHE, APACHE II (**Table 1**), which is currently the world's most widely used outcome prediction score for critically ill patients. APACHE II is simpler than the original system in that there are just 12 physiological variables, and the effects of chronic health status are incorporated directly into the model so that there is only 1 overall score, ranging from 0 to 71. The effect of age is also included. The recorded value for each physiological variable in APACHE II is based on the worst value recorded during the first 24 hours of a patient's admission to the ICU. A score greater than 34 is associated with a mortality rate of more than 80%.

Table 1. Key Components of the Three Main Outcome Prediction Scores

APACHE II	**SAPS II**	**MPM II_0**
Physiological variables	Physiological variables	Physiological variables
Temperature	Temperature	Heart rate
Mean arterial pressure	Systolic blood pressure	Systolic blood pressure
Heart rate	Heart rate	Coma (GCS 3-5)
Respiratory rate	Serum bicarbonate level	Acute diagnoses
Oxygenation (Pao_2 or $a\text{-}aDo_2$)	Pao_2 /Fio_2	Acute renal failure
Arterial pH	Serum bilirubin	Cardiac dysrhythmia
Serum sodium	Serum sodium	Cerebrovascular incident
Serum potassium	Serum potassium	Gastrointestinal bleeding
Serum creatinine	Serum urea or urea nitrogen	Intracranial mass effect
Hematocrit	Urine output	Chronic diagnoses
White blood cell count	White blood cell count	Chronic renal failure
Glasgow Coma Scale score	Glasgow Coma Scale score	Cirrhosis
Age points	Age	Metastatic cancer
Chronic health points	Type of admission	CPR prior to admission
	AIDS	Mechanical ventilation
	Hematological malignancy	Nonelective surgery
	Metastatic cancer	Age

Abbreviations: $a\text{-}aDo_2$, alveolar-arterial oxygen pressure difference; APACHE, Acute Physiology and Chronic Health Evaluation; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; MPM, Mortality Probability Model; SAPS, Simplified Acute Physiology Score.

APACHE III was developed in 1991 and further updated in 1998. APACHE III never gained wide support, partly because it is more complex but also because it was marketed commercially so the software was not freely available. APACHE III was remodeled in 2006, using more refined statistical methods to create APACHE IV, which uses the same physiological variables and weights but different predictor variables. In the validation set of more than 100,000 patients, the area under the ROC curve (ie, the AUC) was 0.88 and the Hosmer-Lemeshow chi-square was 16.9 ($P = 0.8$). APACHE IV also includes ICU length of stay prediction equations, which may facilitate the assessment and comparison of ICU efficiency and resource use.

Simplified Acute Physiology Score

The SAPS, developed and validated in France in 1984, used 13 weighted physiological variables and age to provide an indication of the risk of death of ICU patients. In 1993, SAPS II was developed from a much larger international database of 13,152 patients through the use of logistic regression techniques. SAPS II includes 12 physiological variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and 3 variables related to underlying disease (AIDS, metastatic cancer, and hematologic malignancy) (**Table 1**). As for APACHE II, for the physiological variables, SAPS II takes into account the worst value over the first 24 hours of ICU admission. The calibration (Hosmer-Lemeshow test) of SAPS II on the validation set of 4,783 patients was 3.7 ($P = 0.883$), and the discrimination (AUC) was 0.86.

In 2005, SAPS 3, a completely new outcome prediction model, was created by the use of complex statistical techniques to select and weight variables. A database of 16,784 patients from 303 ICUs in 35 countries was used to develop the score with the aim of increasing representativeness to all countries. SAPS 3 is divided into 3 subscores:

1. Data related to patient characteristics prior to admission (age, comorbidities, use of vasoactive drugs before ICU admission, intrahospital location before ICU admission, and length of stay in the hospital before ICU admission)

2. Data related to the circumstances of the admission (reasons for ICU admission, planned vs unplanned ICU admission, surgical status at ICU admission, anatomic site of surgery, and presence of infection at ICU admission)

3. Data related to the degree of physiological derangement within 1 hour (in contrast to the 24-hour time window in the SAPS II model) before or after ICU admission (lowest estimated Glasgow Coma Scale score, highest heart rate, lowest systolic blood pressure, highest bilirubin concentration, highest body temperature, highest creatinine concentration, highest leukocyte count, lowest platelet count, lowest pH, and ventilatory support and oxygenation)

SAPS 3 thus includes 20 variables in total and the total score can range from 0 to 217. Unlike the APACHE and MPM scores, SAPS 3 includes customized equations for prediction of hospital mortality in 7 geographical regions (Australasia; Central and South America; Central and Western Europe; Eastern Europe; Northern Europe; Southern Europe, the Mediterranean; and North America). SAPS 3 has been shown to exhibit good discrimination, calibration, and goodness of fit.

Mortality Probability Model

The first MPM was developed using data from patients in just 1 ICU and was published in 1985. Unlike the APACHE and SAPS systems, MPM consisted of 2 models: an admission model that included 7 admission variables, none of which was treatment related, and a 24-hour model that included 7 variables reflecting treatments and the patient's condition in the ICU, which was designed for patients who stayed in the ICU for more than 24 hours. A revised model, MPM II_0, was developed in 1993 using logistic regression techniques on a database of 12,610 ICU patients from 12 countries. MPM II also consists of 2 scores: an admission model, MPM_0, which contains 15 variables (**Table 1**), and a 24-hour model, MPM II_{24}, which contains 5 of the admission variables and 8 additional variables. Unlike the APACHE and SAPS systems, in which variables are weighted, MPM II designates each variable (except age, which is entered as the actual age in years) as present or absent and gives a score of 1 or 0 accordingly.

A third version of MPM_0 was developed in 2007 using a database of 124,885 patients from 135 ICUs in 98 hospitals (all in the United States). MPM_0-III consists of 16 variables, all obtained within 1 hour of ICU admission, of which 3 are physiological parameters. These are used to estimate the probability of mortality at hospital discharge.

Comparing Score Performance

As stated earlier, performance of the 3 scores will differ according to how much the population in which they are being used differs from that of the developmental cohort. As such, it is difficult to determine which score, if any, is better globally. In a retrospective study of 11,300 patients from 35 hospitals in California, discrimination and calibration were adequate for APACHE IV, MPM_0-III, and SAPS II, with discrimination of APACHE IV slightly better than that of the other 2 scores (AUC 0.892 for APACHE IV, 0.873 for SAPS II, and 0.809 for MPM_0-III, $P < 0.001$). Customization of scores to the local patient case-mix is one technique that can help improve the calibration in individual countries or regions. In a retrospective analysis of prospectively collected data from a German surgical ICU, the discriminative abilities of SAPS 3, APACHE II, and SAPS II were similar (AUC 0.80 for APACHE II, 0.83 for SAPS II, and 0.84 for SAPS 3) and all 3 scores had poor calibration, which improved after customization to the local population. Similarly, the calibration of APACHE IV improved after customization to a Dutch population (Hosmer-Lemeshow C statistic = 823 before and 147 after customization) without altering the good discrimination. In Austria, poor calibration of the general SAPS 3 score (C = 90.29, $P < 0.001$) and of the SAPS 3 equation for Central and Western Europe (C = 45.61, $P < 0.001$) was reported; after customization, however, calibration was excellent (C = 5.61, $P = 0.847$). Discrimination of all 3 SAPS 3 equations was good (AUC 0.82).

ORGAN DYSFUNCTION SCORES

As the general management of intensive care patients has improved and, with it, survival rates, increasing interest has turned to the ability to assess outcomes other than mortality. Many patients who die in the ICU now do so as a result of multiple organ failure, and the presence of organ dysfunction is associated with prolonged ICU stays and increased use of resources. Organ failure scores, by describing the degree of organ dysfunction in individual ICU patients over time, thus provide an important ongoing measure of morbidity. Many attempts have been made to develop organ dysfunction scores over the last few decades, but we will focus on 2 of the scores most commonly used in general ICU patients: MODS and its successor, SOFA.

Multiple Organ Dysfunction Score

The MODS was developed by Marshall et al and published in 1995. Seven organ systems (respiratory, cardiovascular, renal, hepatic, hematological, central nervous system, and gastrointestinal) were selected for further consideration based on a literature review of 30 manuscripts that had described organ dysfunction, and potential variables that could be used to describe the organs of each system were selected (**Table 2**). No reliable descriptor of gastrointestinal function could be identified, so this system was not included in the final model. For the cardiovascular system, a composite variable, the pressure-adjusted heart rate (Heart Rate × Central Venous Pressure/Mean Blood Pressure) was created. In patients without a central line, this variable is scored as normal. A score of 0 (normal) to 4 (most dysfunction) is given for each organ system, based on the first results for each parameter that day, giving a total maximum score of 24. The score was developed in 336 patients admitted to 1 surgical ICU and validated in 356 patients admitted to the same ICU. The score was later validated in many other groups of patients. Not surprisingly, increasing MODS values correlated well with ICU outcome; in the initial validation study, no deaths occurred in patients with MODS scores of 0, and the ICU mortality rate was 100% for patients with scores of more than 20.

Table 2. Key Characteristics of the Sequential Organ Failure Assessment (SOFA) and the Multiple Organ Dysfunction Score (MODS)

Score	Authors	Year of Publication	Development	Organ Dysfunction Measures
MODS	Marshall et al	1995	Systematic review of the literature	First value of each day Respiratory: PaO_2/FIO_2 Coagulation: platelet count Hepatic: serum bilirubin Cardiovascular: pressure-adjusted heart rate (HR × MAP/CVP) Neurological: GCS Renal: serum creatinine
SOFA	Vincent et al	1996	Consensus	Worst value over 24-h period Respiratory: PaO_2/FIO_2 Coagulation: platelet count Hepatic: serum bilirubin Cardiovascular: blood pressure, need for vasoactive drugs Neurological: GCS Renal: serum creatinine and urine output

Abbreviations: CVP, central venous pressure; GCS, Glasgow Coma Scale; HR, heart rate; MAP,

mean arterial pressure.

Sequential Organ Failure Assessment

Following shortly after the development of MODS, a consensus conference was held in Paris in 1994 that led to the development of SOFA (**Table 3**). Six organ systems (respiratory, cardiovascular, renal, hepatic, central nervous, and coagulation systems) were selected for inclusion. In SOFA the worst value on each day is recorded, unlike MODS, which uses the first value of each day. The function of each organ system is scored from 0 (normal function) to 4 (most abnormal), giving a possible score of 0 to 24. **Table 2** shows the key similarities and differences between these 2 systems.

Table 3. The Sequential Organ Failure Assessment (SOFA) Score

SOFA Score	0	1	2	3	4
Respiration					
Pao_2 /Fio_2, mm Hg	>400	≤400	≤300	≤200	≤100
				with respiratory support	
Coagulation					
Platelets $\times 10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin, mg/dL (μmol/L)	< 1.2 (< 20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mm Hg	Dopamine ≤5 or Dobutamine (any dose)[a]	Dopamine >5 or Epinephrine ≤0.1 or Norepinephrine ≤0.1[a]	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1[a]
Central nervous system					
GCS score	15	13-14	10-12	6-9	< 6
Renal					

Creatinine, mg/dL (µmol/L)	< 1.2 (< 110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (>440)
Or urine output				< 500 mL/d	< 200 mL/d

Abbreviations: GCS, Glasgow Coma Scale; MAP, mean arterial pressure.

[a]Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/min).

Reproduced with permission Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996; 22:707-710. Copyright © 1996. Springer-Verlag.

The conference participants believed that the cardiovascular component of MODS, the pressure-adjusted heart rate, was too complex for daily practice and not sufficiently accurate because it could be normal even in patients with very severe shock. With no other appropriate independent variable available to evaluate cardiovascular function, it was decided to use a treatment-related variable (dose of vasopressor agents). This approach may be considered as a limitation because it is somewhat subjective, depending on local treatment policies and even individual physician preferences. Furthermore, the score may need to be adapted as new therapies are developed and incorporated into clinical practice. For example, vasopressin is now being used more widely as an adjunctive vasopressor agent than was the case when SOFA was developed. The SOFA score could be adjusted in different ways to account for this, for example, by giving additional points to patients who receive vasopressin but not norepinephrine (2 points for vasopressin ≤0.04 U/min and 3 points if >0.04 U/min) or by giving a cardiovascular component score of 3 to patients receiving vasopressin as a single vasoactive agent and a score of 4 to those receiving vasopressin plus additional agents. Interestingly, although SOFA and MODS showed similar performance in terms of mortality prediction, when only the cardiovascular components were used, outcome prediction was better for SOFA in one study.

SOFA was initially validated in a mixed medical-surgical ICU population and has since been used and validated in many different patient groups. Because it is so easy to use and variables are readily and routinely measured in most ICUs, SOFA is now the most widely used of the organ dysfunction scores and has been incorporated as an outcome measure in many clinical trials. Increasing SOFA

scores on admission or during the ICU stay (maximum SOFA score) correlate well with mortality. Moreover, changes in SOFA score over time are useful in predicting outcome; one study reported that regardless of the initial SOFA score, an increase in SOFA score over the first 48 hours of the ICU stay was associated with a mortality rate of 53%, no change in score was associated with a mortality rate of 31%, and a decrease in the score was associated with a mortality rate of 23% ($P < 0.01$). As well as providing a global assessment of total organ dysfunction, the individual organ scores can be considered separately, thus providing a description of patterns of organ dysfunction at any point in time. Increasing SOFA scores for each organ are associated with increased mortality rates.

SUMMARY

Severity of illness scores are now used to some extent by all ICUs, and with increasingly automated data collection, calculation has never been easier. Such scores can be useful to guide in prognostication, to assess ongoing disease development and organ dysfunction, to compare ICU performance over time and across units, and to compare clinical trial populations and outcomes. The various types of scores have been developed for different purposes and should not be considered as mutually exclusive but rather complementary, as each provides different information. Clinicians must bear in mind the limitations of each scoring system when interpreting the results. All of the main outcome prediction scores have been updated to adapt to changing ICU demographics and treatments, and further changes will be needed periodically.

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CHAPTER 50

Principles of Statistics and Evidence-Based Medicine

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A working knowledge of statistics is essential to reading the medical literature, determining the quality of evidence, deciding when to alter practice, and planning new investigations to advance the field. In academic medicine, where one must usually "publish or perish," a working knowledge of statistics is essential for writing abstracts, publications, and grant applications.

This chapter is divided into 2 sections. The first is a primer on basic statistics for the intensivist and describes how data can be described and analyzed within broad principles. This section is not meant to replace an introductory statistics course or text (see "Resources") but provides a background and structure to calculate basic statistics for critical care. The second section is a primer on evidence-based medicine. This section is meant to provide an introduction to the principles of evidence-based medicine in a critical care setting, not to supplant the several excellent references already available.

PRINCIPLES OF STATISTICS

> *Oh, people can come up with statistics to prove anything: 14% of people know that.*

Homer Simpson

Bias and Confounding Factors

Bias and confounding factors undermine careful research and lead to incorrect interpretations of the data. These problems cannot always be eliminated but should always be minimized and discussed.

Bias is a systematic error that reduces the accuracy of results. There are many potential sources of bias:

- In a retrospective review, certain populations can be missed because of the search method (eg, use of diagnosis codes that are not perfectly sensitive or specific) or the availability of data (eg, missing medical records or inability to retrieve images). Efforts to combat this might include using prospective registries, if all patients can be identified, or using automated electronic retrieval of data instead of paper records, if the veracity of routine coding can be assessed.

- Patients who enroll in a clinical trial may be different than those who choose not to enroll, or patients in a study may be enrolled only in referral centers. Thus, enrolled patients may not sufficiently represent the population of interest.

- Patients who are available for follow-up in an observational study may be different from those who are not available, especially if physical presentation is required. Multiple strategies to ensure follow-up (telephone, e-mail, social networking, centralized electronic medical records, vital records) may be necessary to minimize loss to follow-up.

- An observer may be biased toward a treatment and may score subjects who received a particular treatment more favorably. Blinded outcome ascertainment (where the person ascertaining outcomes is unaware of the assignment) reduces this bias. This practice is common in critical care trials, where it is often impossible to blind treating physicians to an intervention (eg, packed red blood cell transfusion, different modes of mechanical ventilatory support, cooling blankets).

- An outcome may be assessed differently by different providers. Validated scores with demonstrated high interrater reliability are mandatory to minimize this.

Confounding factors occur when an unrecognized factor is associated with both the independent and the dependent variables. For example, one might hypothesize that coma after cardiac arrest is associated with poor outcome. This is correct, but the relationship is confounded by the time to return of spontaneous circulation: The longer the time to return of spontaneous circulation, the more likely coma is to occur and the worse the outcome is likely to be. Likewise, the more complicated the relationship between the independent and dependent variables, the more likely an unknown variable will confound the results. Confounding factors often occur in critical care because there are usually variables outside the control of the researcher, even in clinical trials. Confounding variables can be limited or evaluated with complete data and careful analysis but are difficult to eliminate without a randomized trial.

"Pragmatic" clinical trials test the effectiveness of an intervention in a broad, routine clinical practice, as opposed to trials that are mechanistic, but when pragmatic trials are negative it can be more difficult to assess the reason if there is variability in the intervention and how it is monitored.

Choosing a (Null) Hypothesis to Test

Statistical analysis means testing a hypothesis. In statistics, one can test the hypothesis that there is no association between variables. This hypothesis of no association is called the *null hypothesis* and is the default for statisticians. An example of a null hypothesis is "There is no association between coma after cardiac arrest and in-hospital mortality." Some academic journals prefer that the alternative hypothesis be stated: for example, "We tested the hypothesis that time to return of spontaneous circulation is associated with outcome after cardiac arrest."

Choosing the Appropriate Statistical Test

The best time to talk to a statistician is before you start collecting the data. Data that are collected haphazardly, are condensed into a simpler (less meaningful) form, or are incomplete may be useless (of no value) or worse than useless (leading you to an erroneous conclusion).

What Are the Data?

Describing the data is very important. Neurologists ask, "Where's the lesion?" because localization leads to the differential diagnosis. Determining the type of

data you have will help you determine which type of statistical analysis is most appropriate.

Normally distributed data are continuous numbers that cluster around a mean. In most data sets, age, serum leukocyte counts, and serum sodium concentrations are normally distributed.

Nonnormally distributed data are continuous numbers that do not follow a normal distribution. In critical care, serum creatinine is usually not normally distributed, as most patients have a value of about 1 mg/dL and a significant proportion of patients have a higher value (ie, a tail to the right). Values on the Glasgow Coma Scale (a validated scale for the patient's level of consciousness) are often not normally distributed, as many patients have the maximum score of 15 (follows commands, oriented, and eyes open spontaneously), some have the minimum score of 3 (unresponsive), and a few have scores of 9 to 13. Such data are often split into ordered categories, such as quartiles, making them an ordinal variable (see the next paragraph).

Ordered groups are often called *ordinal variables*. The modified Rankin Scale (mRS), a common scale for functional outcomes, is scaled from 0 (no symptoms) to 6 (dead) and is an ordinal variable. Quartiles (lowest quarter to highest quarter) are a common way to express ordered data in groups. Numerical variables are often placed into ordered groups for ease of displaying the data (at the potential loss of some statistical power).

Outcome data are sometimes categorized as "good" versus "poor" outcome. The point at which data are dichotomized should be chosen with caution, because this often leads to some loss of statistical power and may imply differences at a cutoff where none exist. Sometimes these measures are chosen by convention, for example, independent for walking (mRS 0-3) versus dependent for walking or worse (mRS 4-6) or Medicare eligible versus not (<65 vs ≥65 years old). If you dichotomize age at 65 years, for example, you will be able to detect a difference between 64 and 66 years of age but not between 66 and 90 years.

Categories are used for data that cannot be expressed as numbers and have no particular order. Race and ethnicity (Caucasian, African American, Hispanic), residency (internal medicine, surgery, pediatrics), and occupation (plumber, lawyer, cook) are categorical data.

In general, methods for comparing groups with ordinal data and continuous data are more statistically powerful (eg, likely to find a difference if one is actually

present) than methods for comparing dichotomous (yes/no) data. As you plan data collection, consider how you can collect more informative data.

Fit the Test to the Data

The following is intended as a general, not definitive, guide to selecting statistical tests. Common statistical tests are described, although different software packages may use different tests, especially for more advanced statistics. (**Table 1**). Many statistical tests assume that the data meet certain characteristics (ie, *t* tests assume that the data are normally distributed). Often, different tests will give a similar answer, even when assumptions regarding the data are violated. Termed *data dredging*, this practice may produce misleading results and is usually evident to sophisticated reviewers and journal editors.

Table 1. Common Techniques for Analyzing Two Variables

	Normally Distributed Number	**Nonnormally Distributed Number**	**Categorical**
Two groups	*t* test	*U* or other rank sum	Chi-square
Three or more groups	ANOVA	*H* or other rank sum	Chi-square
Normally distributed number	Linear regression	Correlation; categorize and use ANOVA	*t*-test if 2 groups, ANOVA if >2 groups
Dichotomous outcome (1 or 0)	Logistic regression	*U* or other rank sum	Chi-square

Abbreviation: ANOVA, analysis of variance.

If you have numerical data, determine whether the values are normally distributed (clustered around a mean) by examining a histogram for the characteristic bell-shaped curve or by formally testing for normality. The Shapiro-Wilk test is commonly used.[1] In critical care, for example, age is usually normally distributed whereas creatinine level is usually not.

Compare normally distributed numbers between groups with a *t* test or analysis of variance (ANOVA). The *t* test is for 2 groups, whereas the ANOVA permits analysis of more than 2 groups. (An ANOVA of 2 groups will give the same results as a *t* test.) For example, one could use a *t* test to compare age between patients in groups of “alive” versus “dead at discharge” but could use ANOVA to compare age between patients in categories of discharge disposition (home,

rehabilitation facility, skilled nursing facility, or death). A subgroup comparison is appropriate to determine which groups are significantly different only if the overall ANOVA reveals a significant difference between groups. It is not appropriate to individually perform a *t* test manually between each of the groups, because multiple comparisons increase the odds of finding a statistically significant difference (see "What *P* Means"). In the preceding example, there are 4 groups and a total of 6 possible comparisons with a *t* test. Most statistical packages provide a variety of generally accepted means for correcting for multiple comparisons. The Bonferroni and least significant differences techniques are common.

Groups of nonnormally distributed variables cannot be reliably compared with ANOVA but should be compared with a rank ordered test. The values in each group are placed in rank order, and the distribution of the ranks between groups is compared. Common examples are the Mann-Whitney *U* for 2 groups and the Kruskal-Wallis *H* for more than 2 groups. Nonnormally distributed numbers can also be converted into categories (eg, quartiles) for analysis.

Correlation broadly means that 2 or more numeric variables move in line with each other. Positive correlations indicate that variables move together, whereas negative correlations indicate that variables move conversely (eg, as one goes up, another goes down). Different methods are appropriate for normally distributed variables, nonnormally distributed variables, and categorical data. The interrater reliability is a correlation analysis to compare the assessments between more than 1 examiner. Outcomes with high interrater reliability are essential to meaningfully interpret clinical data. For example, if 2 examiners do not agree on the definition of *dependence*, then a clinical study of ICU patients to determine predictors of dependence will be underpowered (see "Power") and difficult to interpret.

Comparison of 2 categories generally should be conducted with the chi-square test (χ^2). This statistical test evaluates the distribution of the frequency of each combination and whether certain combinations occur more frequently than would be expected by chance alone. Although the number of levels within each category may vary, there should be at least 5 subjects for each potential combination. When the frequency of some combinations is low, the Fisher exact test is generally more appropriate. A significant result indicates that 2 categories are associated with each other (see "Odds Ratios and Confidence Intervals").

Linear regression is a measure of association between 2 normally distributed

variables. Linear regression defines a line ($y = \beta + \alpha \times x$) that minimizes the square of the difference from each data point to the defined line. (In this equation, y is the dependent variable, β is a constant, x is the value of the independent variable, and α is the coefficient of the independent variable. If α is significantly different than 0, the analysis is significant.) Like correlation, the relationship can be positive ($\alpha > 0$, the dependent and independent variables increase together) or negative ($\alpha < 0$, one increases while the other decreases).

Multiple linear regression uses multiple independent variables to define the line

$$y = \beta + \alpha 1x1 + \alpha 2x2 + \alpha 3x3.$$

Here, $\alpha 1x1$ is the term for the first independent variable, $\alpha 2x2$ is the term for the second independent variable, and so on. As a guideline, there should be at least 10 cases for every variable in the equation. Not every variable needs to be a normally distributed number, and some variables can be categories or dichotomous variables. In other words, one variable could be a term for age, another a term for gender, and another a term for ethnicity. Nonnormally distributed variables generally should not be entered as regression terms because skewed data may account for a disproportionate amount of variability in the analysis.

Logistic regression determines the probability of a dichotomous (0 or 1) outcome from a continuous independent variable. For example, it is appropriate to determine the probability of an outcome (dead vs alive, dependent vs independent, etc) that is expressed as 0 or 1. Like linear regression, multiple variables can be tested.

Ordinal regression is similar to logistic regression, but the outcome is an ordinal variable. Many outcome scales are ordinal variables, so ordinal regression can give a clearer interpretation of how to improve outcome by 1 step. Ordinal regression makes additional assumptions about the data, specifically proportional odds (the assumption that there are proportional odds for improving each step for changes in the independent variable), and is not always appropriate.

To select multiple independent variables (model building) for regression, first determine which independent variables (inputs) are significantly associated with the dependent variable (output) when only those 2 variables are considered (univariate analysis). Manuscripts typically contain a table detailing univariate associations between independent variables and the dependent variable. A variety of techniques are available for building multivariate models from

significant univariate analyses:

1. Forward—adding variables one at a time, based on the maximum amount of variability explained
2. Backward—starting with all potentially significant variables in the model and subtracting the least meaningful variables one at a time
3. Stepwise—adding variables one at a time, based on the maximum amount of variability explained, and analyzing the model at each step to determine whether any variables in the model have become nonsignificant and should be removed

Multivariate models should be informed by knowledge of the disease and variables known to be associated with the outcome of interest. All models are wrong in that some variability in the data will remain unexplained, but some models are useful in how they assist in interpreting the data. Editors and reviewers usually take a dim view of new models that omit variables already known to be associated with the outcome of interest because they are usually confounded by already known variables. Newly described associations that persist after correction for known variables tend to be of greater interest. Prospectively defined studies will generally prespecify which variables will be corrected for in multivariate models.

Interpreting the Test Results

What P Means

The *P* value (indicating statistical significance) is the probability of finding these results with a true null hypothesis (eg, no difference between groups). *P* is expressed from nearly 0 (extremely unlikely to be attributable to chance) to 1 (attributable to chance). $P = 0.5$ equals a coin flip. The lower the *P* value, the more unlikely the result is attributable to chance alone and the more likely there is a true association between the variables. In clinical medicine, $P = 0.05$ (5%, 1 in 20 trials) is typically considered the critical value for rejecting the null hypothesis. Lower *P* values (0.01 for 1 in 100, 0.001 for 1 in 1,000, etc) indicate that the results are less likely to be attributable to chance.

“Significant” *P* values do not mean that the result is clinically significant; for example, in trials of blood pressure management, differences of 1 mm Hg

between groups can be statistically significant but are hardly meaningful in clinical practice. Significant P values do not mean that the result is unbiased, not confounded, or biologically plausible.

If $P = 0.05$ can be found by chance in every 20 comparisons, large data sets and the electronic retrieval of large numbers of data points allow for unprecedented levels of statistical mischief. Statistical analysis should follow medically plausible hypothesis generation, not the other way around (conducting many statistical tests in a data set and then generating hypothetical questions to the "answers" one has found).

Point Estimates and Confidence Intervals

Parametric statistics for normally distributed variables will provide a point estimate and the confidence interval (CI) around it; in clinical medicine, a 95% CI is standard. The point estimate is the best estimate of the true value of the variable from the analyzed data. One can be 95% confident that the true value lies somewhere within the 95% CI. If a result is statistically significant ($P < 0.05$), then the 95% CI does not include the point estimate of a comparison group or known value.

Odds Ratios and Confidence Intervals

If you are comparing 2 categories, then your point estimate and CI will be an odds ratio derived from the frequencies observed. The value of an independent variable will be said to alter the odds of the dependent variable (or outcome), and one can be 95% confident that the true answer lies within the 95% CI. Significant results at $P < 0.05$ will have a 95% CI that does not include an odds ratio of 1.

Statistical Analysis

Most manuscripts will have a section titled "Statistical Analysis." Although not every manuscript will be easy to understand, most will use straightforward statistical analysis to present the results. If you plan to write for the medical literature, you can use manuscripts in your field as a guide to which analyses are most commonly used.

Power

Statistical tests essentially calculate a signal-to-noise ratio in the data. The signal

is the amount of variability in the data explained by the variables you specify, and the noise is the amount of unexplained variability left, statistically referred to as *error*. Significant variables explain a statistically significant amount of the variability in the data. In multivariate models, no more variables are added to the model when one can no longer explain a significantly greater amount of variability in the data. (If you are using backward selection of variables, you stop taking away variables when doing so leads to significantly more unexplained variability.) More variability in the data (dependent or independent variables) will lead to more statistical error and decrease the likelihood of a significant result (reduced power).

These principles suggest strategies to increase statistical power. Generally, the most efficient strategies are to reduce variability in the data by collecting the most meaningful data points (eg, record the age in years rather than in groups such as <65 years of age and ≥65 years of age), collect data that are more likely to directly affect outcomes of interest, and collect end points with the highest possible interrater reliability (such that everyone agrees on the outcome score for every given patient). More variability in the assessed outcome will reduce the power to determine what leads to any level of outcome. Another strategy is to increase the number of cases studied: Sometimes this is feasible (an electronic search can be extended further back in time), sometimes it is not, and sometimes it merely will be expensive (eg, extending a clinical study).

EVIDENCE-BASED MEDICINE IN CRITICAL CARE

Strengths of Evidence

The data regarding an intervention or risk factor can be of variable strength. Many professional societies grade evidence and regularly publish recommendations on how to manage a given condition.

Expert opinion such as roundtable discussions, recommendations from societies, or surveys of practitioners may be the only data available on a topic. These recommendations are often a starting point or accompany a call for papers. Sometimes interventions that everyone “knows to be true” must remain expert opinion because there is not sufficient uncertainty to justify a clinical trial (eg, volume resuscitation in septic shock is generally accepted, but no one is prepared to conduct a clinical trial that includes withholding such resuscitation as a treatment arm).

Observational, retrospective studies often provide the first data necessary to generate a hypothesis for further research. Typically these hypotheses are made without the data in hand, and the retrospective review involves ascertaining and analyzing the data. Such analyses may start with patients who have been previously identified (such as a disease registry) but without prospective collection of the variable of interest. If the patients have not been identified, the medical records must be found by a search of discharged patients. (Such searches routinely misidentify a substantial number of patients.) When one retrospective analysis has been published, the publication of a confirmatory analysis from a separate sample increases the likelihood of a correct result. Observational, prospective studies generally have higher reliability, less variability in the patient population, and less variability in the data than do retrospective studies.

Certain data can be reliably collected retrospectively or prospectively (ie, laboratory results), whereas other data must be prospectively collected. Clinical events that do not have perfect interrater reliability (pneumonia, clinical vasospasm after subarachnoid hemorrhage, clinical seizures) are best prospectively collected by standardized (even if imperfect) criteria. Numerous data (eg, medication administration records, discrete laboratory measurements) are better obtained by automated methods. Of note, outcomes other than death usually cannot be reliably obtained retrospectively.

Randomized, prospective trials are generally considered the most reliable level of evidence. Multiple randomized clinical trials with the same result are usually considered definitive proof unless later evidence of a confounder, systematic bias, or fraud is discovered.

Meta-analyses combine the results from disparate clinical trials into a single analysis. Some consider meta-analyses of randomized clinical trials to be the most reliable level of evidence. (As always, the devil is in the details, in this case the collected data.) A forest plot is used to display the results from several studies on a single graphic so that the relative size, point estimate, and CI for every trial can be seen. Most investigators also analyze the heterogeneity of the data, a measure of how different the study results are from each other—the more heterogeneous the data, the less certain the effect.

Clinical Trials in Critical Care

Even the most persuasive hypotheses and biological rationales can fail (and

sometimes do) in pivotal clinical trials. For new drug approval in the United States, the general standard of two prospective randomized clinical trials makes a real treatment benefit more likely, although it delays approval and increases costs. The standard for devices is different and requires fewer data. Many new devices are approved in the absence of clinical investigation for safety and effectiveness because they are considered substantially similar to already approved devices. The relative benefits of drug versus device approval standards are beyond the scope of this chapter.

Clinical trials in critical care are notoriously difficult for a variety of reasons. Ascertainment times are typically quite short (hours instead of days or months) because patients must be treated quickly or the disease will be treated (either effectively or not) outside of the study. Patients are often unable to consent because of altered consciousness, and so consent must be obtained from a legally authorized representative or deferred. Deferred or implied consent for critical care trials is rarely allowed but may be allowed when the disease is deadly, consent would be so impractical as to meaningfully prevent the research, the treatment carries relatively low risk, and substantial oversight is available (contact your local ethics board for details). Some have called for an end to most clinical trials in critical care in favor of registries and observational studies given these serious difficulties.

Phase 1 studies[2] are preliminary studies of new drugs for which the effective dose and potential side effects are not well described. Phase 1 studies enroll small numbers of patients (typically <10) and often progressively increase the dose of drug to determine the optimal dose and record a preliminary incidence of adverse events.

Phase 2 studies are for drugs whose dosage has been established. Phase 2 studies typically are small to medium trials, with fewer than 100 patients, that are designed to obtain safety and preliminary efficacy measures.

Phase 3 trials are pivotal clinical trials to test the efficacy of an intervention. These trials can involve hundreds or thousands of patients and typically involve multiple recruiting sites. Protocol adherence, ascertainment of adverse events, blinding, and reliable reporting of outcomes are key to the successful execution of these trials.

Phase 4 studies are conducted after device or medication approval. They may test the effectiveness of an intervention in a general population as opposed to the

efficacy in the defined patient population of a clinical trial. Phase 4 studies can be interventional or observational, single center or multicenter.

Collecting Data for Critical Care Research

Regulatory Approval

Institutional review boards are responsible for the oversight of human subjects research in the United States; in the European Union, the Declaration of Helsinki usually applies. Regardless of location, some sort of human subjects protection and oversight is mandatory prior to starting clinical research. Approval will likely come with varying degrees of oversight, depending on the type of research. Research on the medical records of discharged patients may be permitted to proceed with minimal oversight and may be exempt from privacy regulations, whereas randomized trials require regular status reports and notification of adverse events that may be related to the study.

Drug approval must be obtained in advance for interventional studies. Physicians may prescribe any approved medication without regard to its approved indication (so-called "off-label" use), but this does not hold true for research. Off-label research use of a medication must be approved in advance. In the United States, this requires clearance and approval from the US Food and Drug Administration (FDA) and an investigational new drug application. Device approval for off-label use requires a similar process and is termed an *investigational device exemption.* The FDA has a limited time to respond to such requests. (Further details are available on the FDA website.[3])

Conflicts of Interest and Research Integrity

A conflict of interest does not prevent research but must be disclosed in advance. Conflict of interest can be directly financial (payment by a sponsor who hopes for a specific result), potentially financial (a wanted result may lead to a later consulting contract or grant), professional ("publish or perish" in academic medicine, advancing one's career), or personal (contradicting an intolerable competitor in the field). A range of reporting standards exist, from the disclosure of any potential or actual financial or professional gain to disclosure of only monetary gains above a threshold. For a given study, different institutions (a medical school, a sponsor, a funding organization, a journal) may require different standards of disclosure. When in doubt, it is generally better to disclose and let the reviewers and readers decide rather than later be accused of hiding

something.

Past suppression of unwelcome results by study sponsors[4] has led to the requirement that all prospective clinical trials be prospectively registered, along with the source of funding. Prominent medical journals have agreed not to publish the results of studies in the absence of prospective registration.

After publication, data and paper forms should be kept for several years (per the publishing journal's policy) in case questions about the data are raised. The ability to reexamine data is an important safety check that prevents error and fraud from remaining unchallenged in the medical record. Questions about published data recently led to the uncovering of data that are unsubstantiated and seem to be fraudulent.[5] In another case, a paper was retracted (and the researcher was later disbarred) after research was found not to conform to accepted standards.[6] A study regarding computed tomography scanning for lung cancer[7] has been undercut by misplacement of the large majority of consent forms and by questions about tobacco industry financing through a trust.[8] In general, the more dramatic the findings and the broader the implications, the more scrutiny the work will receive and the more others will look to confirm, refute, or build upon it. Funding agencies may mandate a data sharing agreement so that others can repeat the analysis or propose other analyses.

If your published results generate interest and hold up under further scrutiny, then your work will be reliably cited. If your results are largely contradicted, everyone will move on. It is generally accepted that even when good work is done by reliable professionals according to accepted standards, there will be occasional missteps. Initially promising results will not be confirmed and hypotheses that seem persuasive will fail in pivotal clinical trials. It is not acceptable, however, to manipulate the data to get the result you are convinced you should see. Reviewers, editors, and their consulting statisticians have a keen eye for data dredging. This is another reason that simple statistical tests are often best: If you perform a complicated analysis where a simple one would do, this will lead to suspicion. The purposeful publication of false results will eventually be revealed as others try to replicate the study and will likely affect the reputation of the investigators and perhaps lead to sanctions.

A published manuscript is more like a sentence in a conversation than a declarative statement and last word. The most influential manuscripts provide the basis for more high-impact research rather than end a line of inquiry.

SUMMARY

When reading the medical literature, note the data collected, the statistical analysis performed, and the presentation of results.

When planning your research, carefully consider the data you will collect. Obtain regulatory approval before you start. Once the data are collected, select the statistical analysis that is most appropriate for the data. Keep the analysis relatively conservative.

The strength of data depends on how they were collected, their statistical significance, the magnitude of their effect, and whether they have been (or can be) reproduced in another sample.

RESOURCES

The University of California at San Francisco maintains a helpful list of statistical resources: www.epibiostat.ucsf.edu/biostat/sites.html.

The US Centers for Disease Control and Prevention and its Wonder program make a wide variety of information available: http://wonder.cdc.gov.

International Committee of Medical Journal Editors describes uniform requirements for submitting data for publication: www.icmje.org.

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CHAPTER 51

Ethical Concerns in the Management of Critically Ill Patients

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Key words: autonomy, beneficence, nonmaleficence, justice

Medical ethics entails the study of moral issues related to the practice of medicine. Questions about the behaviors of healthcare providers, the decision-making process, and stakeholders' values, rights, and responsibilities generate ethical reflection that requires a thorough understanding of philosophical concepts, religion, and the jurisdictional laws.

Most texts in medical ethics are written from Western perspectives, which are primarily based on Judeo-Christian philosophical traditions. Japanese and Chinese medical ethics may have different emphases and priorities, so becoming acquainted with the jurisdictional cultural trends and laws is an important step toward becoming proficient at dealing with ethical issues in the ICU.

When the possibility of significant disability or even death arises, it is difficult to predict how fears of future outcome will ultimately alter the predefined preferences of an individual patient or his or her surrogate decision maker.

When issues relating to advance directives and the withholding and withdrawal of life-supportive therapy arise, clinical prognostic questions require specific answers, so clinicians should attempt to achieve the highest level of certainty regarding the diagnosis and prognosis with the patient's wishes in mind.

PRINCIPLES OF ETHICS

Autonomy

Autonomy is defined as the ability to self-rule, self-determine, or self-govern. Personal autonomy requires, at a minimum, self-rule that is free from coercion from others or from limitations such as inadequate understanding that prevent meaningful choice. This principle supports the notion that rational individuals with decisional capacity (or competency in legal terms) are uniquely qualified to decide what is best for themselves. This also means that people should be allowed to do whatever they want, even if doing so involves considerable risk or would be deemed foolish by others, provided that their decision does not infringe on the autonomy of another. Courts have routinely upheld the right of competent persons to refuse lifesaving interventions such as blood transfusions because either medical therapies in general or specific therapies are prohibited by the patient's religious or moral beliefs.

The universal right of respect for a patient's autonomy is rooted in the rulings from the Nuremberg trials, known as the Nuremberg Code, which is the basis of modern statements of human rights such as the Declaration of Helsinki and the Belmont Report. These landmark statements support and guide the basic requirements of voluntary informed consent and the individual's right to refuse treatment or participation in research. Additionally, a patient's right to confidentiality is based on the principle of autonomy. In general, people have no legal obligation to keep other people's secrets, but in the practice of medicine, we have both a moral and a legal obligation to protect our patients' confidential information.

Beneficence

The principle of beneficence is inherent in the role of physicians and healthcare providers and determines our duty to prevent evil or harm by promoting good and enhancing the welfare of others. In conjunction with autonomy, promoting the welfare of others is the foundation of the physician-patient relationship, as morality requires not only that we treat persons autonomously and refrain from doing harm but also that we contribute to their well-being. Similarly, physicians and healthcare providers are required to balance benefits, risks, and costs to improve the welfare of people overall. As such, the role of physicians and healthcare providers as promoters of well-being involves not only their patients but the community as a whole.

In certain circumstances, physicians may be morally and legally obliged to supersede the physician-patient relationship. Some jurisdictions, for example, require that physicians report clinical situations that may be associated with risks

to other citizens, such as reporting a newly diagnosed epilepsy case to a governmental office of motor vehicles. Similarly, when physicians believe or fear that a patient may be dangerous to another person, a duty to prevent evil or harm may be invoked. In the case of Tarasoff (*Tarasoff v Regents of the University of California,* 551 P2d 334 [1976]), the court recognized the duty of a physician to warn another person of a dangerous patient's intent to harm that person even if this meant violating the patient-physician confidentiality agreement. One's perceptions and intentions—even if in the best interest—should not supersede the wishes or well-being of another competent human being.

Nonmaleficence

The principle of nonmaleficence was introduced by Beauchamp and Childress. This principle establishes the duty to refrain from inflicting harm on others and is sometimes defined by the maxim *primum non nocere*. Obligations of nonmaleficence include not only duties not to inflict harm but also duties not to impose risk or harm. In cases of risk imposition, both the law and morality recognize a standard of *due care* that determines whether the agent who is causally responsible for the risk is legally or morally responsible as well. This standard is specific to the principle of nonmaleficence. Understanding of what lack of due care implies is what defines negligence. The line between due care and inadequate care is often difficult to draw. Specific situations in the ICU that relate to the principle of nonmaleficence and lack of due care include withholding and withdrawal of life support, extraordinary (or heroic) treatments, sustenance of technologies and medical treatments, intended effects and merely foreseen effects (theory of double effect), and situations in which definitions of *killing* versus *letting die* may become nebulous.

Justice

The principle of justice demands that one act to promote the greatest benefit to the greatest number of individuals while inflicting the least amount of harm. This principle stipulates that similar cases be treated in a similar manner, that the benefits and burdens be shared equally within society, that goods be distributed according to need, that individuals be rewarded for contributions made, and that the degree of effort determine an individual's reward.

WHAT IS ETHICAL?

This is a difficult question, and every individual is ultimately responsible for making his or her own morally correct decisions and implementing them. To this end, ethical dilemmas emerge because of a conflict between moral values, and their interpretation, among the agents involved in the decision-making process. There are several “rational” ways of approaching ethical dilemmas that are characterized by a systematic and reflective use of reason in the decision-making process: principlism, deontology, consequentialism and utilitarianism, and virtue ethics.

TREATING PATIENTS IN THE ICU

Consent for Treatment

The concept of informed consent stems from a principle of personal autonomy. This principle, well guarded by the US Constitution, allows for moral self-determination and is based on two important elements: voluntary choice and decisional capacity. It represents the ultimate overt expression of individual human rights. Technically, medical professionals can determine decision-making capacity but lack the legal authority to determine competence; however, their assessment of decision-making capacity serves not only as a guide for many legal determinations but also as the functional equivalent of such determinations in the absence of legal proceedings.

In the United States, the legal doctrine of informed consent incorporates a third element: the disclosure of information, without which voluntary choice and competence cannot be properly exercised. However, excessive emphasis on the disclosure requirement may undermine the implementation of informed consent. It is the physician’s finding of incapacity that causes alternative forms for obtaining consent to be sought and a patient’s legal rights to be temporarily suspended without the involvement of the court. Frequently in the ICU, critical care specialists encounter situations where patients seem to lack decision-making capacity. This is why, according to Bateman-White et al, “it is critical that physicians learn to apply the standards of assessment of decisional capacity that are used to arrive at a legal determination of competence” and facilitate the institution of medical therapies.

But how can we assess decision-making capacity in emergency situations, and particularly in critically ill patients? According to Akinsanya et al and Beauchamp and Childress, to determine whether a patient lacks capacity, a

physician must establish that the subject is able to (a) understand the information relevant to the decision; (b) retain that information; (c) use or weigh that information in making the decision, including information about the reasonable and foreseeable consequences of deciding one way or another or failing to make the decision; and (d) communicate the decision (whether by talking, using sign language, or any other means). However, determining all of these points may be difficult in critically ill patients, because evidence shows that even in the absence of cognitive impairment, acute illness can impair the understanding of disease and especially the concepts of proportionality and risk. Given this, it has been suggested that a procedure for capacity assessment be developed and standardized. Such a procedure should include determining whether the patient understands concise points, such as the diagnosis; assessing the proposed treatment, including the risks and potential benefits of the treatment and its alternatives; and outcome statistics.

Decision Making in the ICU

When a critically ill patient is deemed not to have capacity, the physician must seek an alternate pathway to determine how to obtain consent and proceed with medical interventions. The options in these cases are to determine whether the patient has drafted an advance directive such as a living will or durable power of attorney (for healthcare) or, in the absence of an advance directive, to seek the substituted judgment of a proxy, family member, friend, or surrogate authorized by the state law. Should the physician be unable to identify an alternative form of consent, the physician must choose to invoke a *best interest standard*. In the case of an emergency, a justification for treatment using the *doctrine of implied consent* may be applied. In nonemergency cases, an ethics or risk management consultation (with the hospital's legal office) is advisable. Physicians are always encouraged to request ethical and legal counseling when treating incapacitated patients who require medical care and are specifically *unbefriended*, meaning that they have no legally authorized surrogate, family member, or friend willing or able to speak on their behalf.

Decision Making and Competency

These are terms that may be used interchangeably. Technically, medical professionals can determine decision-making capacity but lack the legal authority to determine competence. However, their assessment of decision-making capacity serves not only as a guide for many legal determinations but

also as the functional equivalent of such determinations in the absence of legal proceedings. Competency is defined as the ability to perform certain tasks and the ability to make a decision. A competent individual must be able to perform well in the following capacities: (a) understand the information, (b) understand the current situation and its consequences, (c) rationally consider information in light of one individual's values, and (d) make an informed decision. It is the physician's finding of incapacity that causes alternative forms of consent to be sought and a patient's legal rights to be temporarily suspended without the involvement of the court.

Disclosure

In the United States and its jurisdictions, the legal doctrine of informed consent incorporates a third element, the disclosure of information. Without disclosure, voluntary choice and competence cannot be properly exercised. In clinical practice and research, excessive emphasis on the disclosure requirement may undermine the implementation of informed consent. A frequently expressed issue regarding the consenting process is that too much disclosure may produce anxiety in the patient and impose an undue influence to agree to a particular therapy or to participate in research. This may be particularly true in critically ill patients whose decisions made under duress may be clouded with misinformation. Nevertheless, the Declaration of Helsinki, the most widely recognized code of ethics related to human research, explains that subjects must receive information concerning the objectives, methods, benefits, and potential harms of the study at hand. The main problem with the enforcement of disclosure in research is that although institutional review boards (IRBs) monitor the inclusion of relevant information pertaining to the study, there is no oversight of what investigators tell prospective research subjects. Other potential conflicts of interest such as financial relationships between industry and investigators, or if financial incentives to enroll subjects and maintain them in the study have been provided may need to be scrutinized by the IRB.

Understanding

Understanding refers to the patient's ability to comprehend propositions related to the intervention or treatment being sought or to understand the implications of participation in research in the setting of his or her condition (objectives, risks, benefits, alternatives, and potential outcomes). Appropriate understanding depends on several factors, including level of intelligence, language skills, attention, orientation, recall, and memory. When approaching patients to obtain

consent for procedures or participation in research, healthcare professionals must determine each patient's level of education to appropriately convey the necessary information. Similarly, disclosure of information related to the proposed intervention in the form of statistics may be helpful. Patients with appropriate understanding can discuss the differences between proposed interventions and alternatives.

Voluntariness

The universal right of respect for a patient's autonomy is rooted in the rulings from the proceedings of the Nuremberg trials of 1947. These are the basis of modern statements of human rights and serve as guidance to the basic requirements of voluntary informed consent and the individual's right to refuse treatment or participate in research. The informed consent process should be guided by the freedom to act voluntarily, without coercive forces or undue influence. Several issues that arise regarding the delivery of care or consent for research may impede voluntariness in critically ill patients. First, the natural setting of critical illness can lead to confusion, inability to evaluate concepts (eg, risk-benefit ratio), and delirium, which may impede the appropriate consent process for clinical care and research. Second, the frightening setting of the ICU may impose coercive forces in subjects who need emergency treatments or who have terminal illnesses if patients believe they have little choice but to be treated or participate in the proposed research. Third, the enthusiasm of the practitioner or investigator could lead to undue influences by manipulation of the information or incomplete disclosure.

Implied Consent

When available sources for consent are lacking, a legal exception to the requirement of direct consent may be invoked in emergency situations in which consent of a reasonable person to an appropriate treatment can be assumed. In a few life-threatening conditions, such as sepsis or myocardial infarction, patients can be involved in the consent process, and risks, benefits, and alternatives to the proposed intervention can be discussed. However, physicians often use the principle of implied consent to perform lifesaving interventions in patients who lack decision-making capacity or surrogates. The emergency doctrine of implied consent allows providers to deliver lifesaving interventions if the failure to perform such interventions in a timely way could potentially lead to increased morbidity and mortality. If the following conditions are met, the physician can use the doctrine of implied consent: (a) the treatment in question represents the

usual and customary standard of care for the condition being treated, (b) it would be clearly harmful to the patient to delay treatment awaiting explicit consent, and (c) patients ordinarily would be expected to consent to the treatment in question if they had the capacity to do so.

Advance Directive or Living Will

The advance directive or living will is probably the best tool to direct care in the event of incapacity, but it is most helpful in end-of-life situations related to terminal conditions, futile care, and multiple-organ dysfunction. These documents can have shortcomings related to care in the ICU: (a) the physician may not find instructions that clearly guide a treatment decision about particular therapies pertinent to ICU care (central lines, chest tubes, renal replacement therapy, thrombolysis, etc) and (b) the ethical argument can be made that a patient can't predict his or her own reaction when faced with disability. Studies have demonstrated a tendency among nondisabled people to view a disabling condition as equivalent to death, and historically, quality outcomes research has frequently combined death with the severe disability group. For example, quality of life after acute ischemic stroke may be seen as high even in the setting of respiratory failure with ventilator dependency. This may be explained by the transforming potential of a phenomenon called *response shift*, where patients redefine their personal values and their sense of reaction when facing disability. In this sense, advance directives or living wills, even if legally valid, may be suboptimal for finding treatment directions in critically ill patients, particularly given that goals of self-determination and perceptions that guide one's chosen moral course may change.

Substituted Judgment Standard

Obtaining informed consent by an authorized surrogate decision maker is an alternative to gaining direct informed consent. Appointees by advance directive, living will, or durable power of attorney (for healthcare decisions) or family members identified by state law are expected to make the same decisions as the patient would if the patient's capacity were intact. This idea of substituted judgment is widely accepted as a valid means of respecting patient preferences. Shortcomings of the substituted judgment standard are related to the poor accuracy of the proxy's ability to predict the patient's will, which some studies have found to be no better than random chance, and the inherent difficulty of making therapeutic decisions for other persons, which may make proxies reluctant to participate in the consent process and may lead them to defer to the

physician's expertise without even considering the full disclosure of risks and benefits associated with the intervention. Particular to cases of withdrawal of life support (discussed subsequently), this standard is based on landmark court decisions in cases such as Karen Quinlan, an alleged incompetent (70 NJ 10 1976). In this case, the Supreme Court of New Jersey established the concept of *substituted judgment standard.* The court determined that a guardian *ad litem* (appointed by court order) was not necessary to represent a patient independently in a particular case and allowed family members to make decisions on the patient's behalf. The ruling is rooted in an individual's legal right to privacy and the notion that a family member can make the assertion based on the family's best judgment (substituted judgment standard). The decision included legal immunity for the physicians and the suggestion to involve ethics committees in such cases.

Best Interest Standard

When one is making decisions for patients who lack decision-making capacity and have no discernable preferences, widespread support exists for using the best interest standard, which was introduced to give some standing to the interests of incapacitated patients independent of their family or guardians views. According to Loretta Kopelman, "The best interest standard should be understood as an umbrella covering different usages. First, it could be used to express moral, legal, medical, or other social goals or ideas that should guide choices. Second, it can be used in making practical and reasonable decisions about what should be done in a particular situation, given the available and usually less than ideal options." Pertinent to incompetent or incapacitated patients, the basis of this standard is framed by landmark court decisions such as that of Conroy (*In re Conroy,* 486 A2d 1209 [NJ 1985]). In this case, the Supreme Court of New Jersey permitted the use of the best interest standard to allow the guidance of therapy for an incapacitated patient whose guardian did not know the patient's explicit wishes for a particular situation. This principle is also applicable in cases where the burden of a therapy outweighs the benefits and the pain of interventions, which would make them inhumane. Some of the shortcomings of using the best interest standard are the possibility that the physician will be judged as paternalistic and the possibility that some will find the principle to be vague and open to abuse, based on the inherent interpretation that it can guide decision makers to do whatever they happen to think is best.

Principle of Clear and Convincing Evidence

In some jurisdictions, the principle of clear and convincing evidence may be used in lieu of the substituted judgment standard when one is dealing with issues pertaining to withholding or withdrawing life-supportive therapies, and it may be applied to comatose patients or patients in persistent vegetative states. This is one of the three main principles used in the US legal system (the other two being *beyond reasonable doubt* and *preponderance of evidence*). This principle can be used by physicians in certain states (Missouri, New York, and Florida, among others) to withdraw life support or any other intervention when there is clear and convincing evidence of a patient's previous statements and in the absence of a declaration such as a living will, advance directive, or durable power of attorney. The decision is based on *Cruzan v Director, Missouri Department of Health* (497 US 261), where the court endorsed the right of a competent person to refuse medical therapy even if this results in the patient's death; more important, the court's ruling was based on the liberty interest set forth by the Fourth Amendment of the US Constitution. The case of Terri Schiavo (*Schindler v Schiavo,* 866 So2d 140 [Fla Dist Ct App 2004]) was ruled following the same principle and endorsing Cruzan's historic court decision.

Ethics Consultations and Court-Appointed Guardianship

In many jurisdictions, if no surrogate or agent is present to act on the patient's behalf, an ethics or risk management consultation (with the hospital's legal office) is advisable. The ethics team can represent the patient's interests by hearing the recommendations of the treating physician or healthcare providers and then deciding whether the recommended treatment plan is ethically permissible and in the patient's interests. This process is usually done with a representative of the hospital's law office. Additionally, in some jurisdictions, and in the absence of surrogate decision makers, physicians must seek representation of the patient's interests in the decision-making process through a court-appointed guardian *ad litem.* Emergency guardianship can be requested through consultation with the hospital's legal team and the ethics committee. One problem with this system is that court-appointed guardians are often unfamiliar with the patient and have little contact with the medical professionals treating the patients. Interestingly, in a study involving homeless persons who lacked family, 80% of subjects indicated that they would prefer a physician rather than a court-appointed guardian to make such decisions. Some jurisdictions allow for hospitals or ethics committees to act on behalf of the patient; likewise, treatment can be determined through concurrence with a second physician who is not directly involved in the patient's healthcare and

does not serve in a capacity of decision making. The American Medical Association has recommended either the involvement of an ethics committee or, like the American College of Physicians, a judicial review for unbefriended patients.

Withdrawal or Withholding

When one is facing withdrawal or withholding of medical interventions, ethical questions cannot be addressed successfully unless the probability of outcomes is entertained. Critical care specialists should make every effort to acquire the highest level of certainty regarding the diagnosis, disease severity, and prognosis with the patient's wishes in mind. The effort will require a thorough knowledge of the literature and a multidisciplinary team approach to attain a balanced view of the impact of therapeutic decisions and the expected disability on the patient. In addressing these issues, we must answer several clinical prognostic questions: What is the probability of death during the next month and next year (and what are the confidence intervals around that probability)? What are the likely causes of death during the first month and subsequently? If the patient survives, what level of disability and handicap will she or he suffer? What impact will the intervention have on survival and/or disability? Advance directives, the substituted judgment standard, the best interest standard, and the clear and convincing evidence principle may be applied in these circumstances.

Is There a Difference Between Withdrawing and Withholding?

The approach to this question is generally guided by the ethical principles of beneficence, nonmaleficence, and distributive justice; the legal implications of due care and negligence; and strong religious views. Patients, family members, and physicians and healthcare providers may have strong arguments on this issue. Some may feel comfortable with both withdrawing and withholding, and some may feel comfortable when deciding not to start a therapy but may feel uncomfortable deciding when to stop that therapy, or vice versa. The US court system has examined this controversy and has noted that withholding a therapy can be based on an active or inadvertent omission. However, the moral and legal implications are based on the issue of *intent*. If one has a duty to treat but actively or inadvertently omits an effective therapy, then one can be found negligent by the court system; but fundamentally, both acts are similar in that the treatment is never started. In the case of Earle Spring (*In the Matter of Earle Spring,* 405 NE 2d 115 [Mass 1980]), a Massachusetts court commented on the

issue of continuing renal replacement therapy in an elderly woman: "The question presented by . . . modern technology, once undertaken, is at what point does it cease to perform its intended function?" In this ruling, the court upheld the concept that physicians have no duty to continue ineffective therapies and concluded that its position was consistent with a moral responsibility.

In practice, when physicians and healthcare providers encounter these situations, some feel morally responsible for the effects of withdrawing care; others may find that there is no difference and therefore will feel no moral responsibility for the end results. According to Beauchamp and Childress, "Feelings of reluctance about withdrawing treatments are understandable, but the distinction between withdrawing and withholding is morally irrelevant and can be dangerous." In regard to life-sustaining therapies, other courts have upheld the concept that there is no difference between withdrawing and withholding.

Very frequently in the ICU, physicians and healthcare providers do not know whether a therapy will be effective. In this case, it would be better to attempt a trial of medical therapy by setting goals of care, determining whether those goals can be achieved by ongoing reassessment, and allowing the ICU team to determine whether the therapy is effective or ineffective while maintaining good communication with patient's family, friends, and/or surrogates. This approach would allow the physician or healthcare team to withdraw an ineffective therapy rather than withhold a potentially beneficial treatment, limiting the chance for undertreatment and avoiding ethical dilemmas.

Finally, according to the World Health Organization, health in its broader sense is defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity," a goal that is sometimes difficult to achieve in the ICU. This is echoed by the words of Hippocrates: "The purpose of medicine is to do away with the sufferings of the sick, to lessen the violence of their diseases, and to refuse to treat those who are overmastered by their diseases, realizing that in such cases, medicine is powerless." In such cases, treatment may be considered futile. According to the Society of Critical Care Medicine's Ethics Committee, treatments that offer no physiological benefit to the patient and therefore fail to achieve their intended goal may be considered futile. Additionally, the committee has advised against treatments that are unlikely to confer any benefit, treatments that are possibly beneficial but extremely costly, and treatments that are controversial and of uncertain benefit.

SUMMARY

Medical ethics deals with moral issues related to daily practice of medicine. Questions about the behaviors of physicians and healthcare providers, the decision-making process, values, rights, and responsibilities generate ethical reflection that requires a thorough understanding of philosophical concepts, religion, professional societies' position statements, and the law. The principle of autonomy, professional responsibility, and the common law require physicians and other healthcare providers to obtain consent before giving any treatment. A medical treatment or procedure must be adequately explained, and the patient must have the capacity to consent to it. If a patient does not have decision-making capacity, emergency treatments must be given using alternative forms of consent. In the case of life-threatening conditions when there exists the possibility of significant disability or death from complications, it is difficult to predict how fears of future disability will ultimately alter the predefined preferences of an individual patient or surrogate decision maker. In issues relating to advance directives and withholding and withdrawal of life support therapy, clinical prognostic questions require specific answers, so caregivers should strive to achieve the highest level of certainty regarding the diagnosis and prognosis with the patient's wishes in mind.

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